OBSERVATIONS

Cardiovascular Biomarkers, Cardiac Dysfunction, and Outcomes in Patients With Type 2 Diabetes: A Prospective, Multicenter Study

Although diabetes is a major risk factor for ischemic heart disease or heart failure (HF), and despite the fact that echocardiography has revealed a high prevalence of left ventricular (LV) diastolic and systolic dysfunctions and hypertrophy (1–3), routine screening for cardiovascular disease using echocardiography in asymptomatic patients with type 2 diabetes is not recommended by current guidelines (4). The availability of laboratory markers of cardiovascular risk would substantially contribute to the early and simple screening of patients at increased risk of HF, allowing them to be better targeted with appropriate pharmacological therapies (5). As part of the LV Dysfunction in Diabetes (DYDA) study, we assessed the relations between different laboratory markers, including centrally assayed glycated hemoglobin (HbA_{1c}), N-terminal probrain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hsCRP), and urine albumin/creatinine ratio (UACR), with clinical conditions and 2-year outcomes in 960 outpatients who were older than 45 years, had type 2 diabetes diagnosed based on World Health Organization criteria, were free of symptoms or signs of cardiac disease, and were enrolled in 37 Italian diabetes care units (2,3).

Patients (61 ± 8 years old) were overweight (34.7% had a BMI ≥30 kg/m^2), with a median diabetes duration of 7 years (range 4–13) and visceral adiposity (waist circumference 99 ± 11 cm). Of these patients, 58.9% had a history of treated hypertension; diabetic retinopathy was present in 12.6%, and renal dysfunction (estimated glomerular filtration rate <60 mL/min/1.73 m^2) was present in 8.5%. Biomarker concentrations were within the normal range in almost half of the patients (median values: NT-proBNP 36 ng/L, hsCRP 1.7 mg/mL, UACR 7.8 mg/g).

Patients with elevated LV mass at baseline and a history of treated hypertension had significantly higher levels of NT-proBNP, hsCRP, and UACR but not HbA_{1c} (Table 1). Combined systolic and diastolic LV dysfunction was associated to higher

Table 1—*Levels of biomarkers by history of hypertension and LV structural and functional characteristics as assessed by ECG and echocardiography at baseline*

Variable	Category	NT-proBNP (ng/L)	hsCRP (mg/L)	UACR (mg/g)	HbA_{1c}, % (mmol/mol)
History of treated hypertension	Yes (*n* = 565)	42 (19–79)	2.0 (0.8–4.2)	8.9 (3.2–29.2)	6.7 (6.0–7.0) (50 [42–53])
	No (*n* = 395)	29 (15–57)	1.4 (0.7–2.9)	6.3 (1.5–17.3)	6.7 (6.0–7.0) (50 [42–53])
	P	<0.0001	<0.0001	0.002	0.97
LV hypertrophy on ECG	Yes (*n* = 37)	70 (31–94)	2.1 (1.0–3.3)	25.3 (4.5–39.3)	6.8 (6.0–8.1) (51 [42–65])
	No (*n* = 841)	35 (16–67)	1.7 (0.7–3.9)	7.4 (2.4–20.9)	6.7 (6.0–7.6) (50 [42–60])
	P	0.002	0.38	0.019	0.46
LV mass	<51 g/m$^{2.7}$ (*n* = 589)	33 (16–63)	2.2 (1.0–5.2)	7.9 (3.2–19.8)	6.8 (6.0–7.6) (51 [42–60])
	≥51 g/m$^{2.7}$ (*n* = 159)	50 (20–97)	1.5 (0.7–3.6)	10.3 (4.7–33.3)	6.7 (6.1–7.7) (50 [43–61])
	P	0.0001	0.0005	0.01	0.99
LV ejection fraction	>50% (*n* = 688)	35 (16–65)	1.7 (0.7–3.8)	8.3 (3.2–23.8)	6.7 (6.0–7.6) (50 [42–60])
	≤50% (*n* = 21)	75 (44–107)	2.1 (1.0–4.9)	11.7 (3.3–50.8)	6.8 (6.0–7.7) (51 [42–61])
	P	0.002	0.47	0.30	0.98
MFS	≤15% (*n* = 243)	39 (17–69)	1.8 (0.9–4.5)	11.8 (4.3–32.3)	6.8 (6.1–7.8) (51 [43–62])
	>15% (*n* = 466)	35 (16–67)	1.6 (0.7–3.3)	7.2 (2.4–19.0)	6.7 (6.0–7.5) (50 [42–58])
	P	0.32	0.054	0.0003	0.07
LV dysfunction*	Isolated LV systolic dysfunction (*n* = 151)	38 (14–63)	1.7 (0.9–4.7)	11.7 (4.5–32.3)	6.7 (6.1–7.9) (50 [43–63])
	Isolated LV diastolic dysfunction (*n* = 148)	33 (15–64)	1.5 (0.7–3.3)	7.5 (1.4–17.7)	7.0 (6.3–7.7) (53 [45–61])
	Combined LV dysfunction (*n* = 87)	42 (22–84)	1.8 (0.8–4.4)	12.1 (3.5–29.8)	6.8 (6.1–7.6) (51 [43–60])
	No LV dysfunction (*n* = 301)	36 (17–69)	1.7 (0.7–3.4)	6.6 (3.0–19.0)	6.5 (5.8–7.4) (48 [40–57])
	P	0.39	0.35	0.005	0.008

Biomarker concentrations shown as median (Q1–Q3). *LV systolic dysfunction was defined as LV ejection fraction ≤50% or midwall fractional shortening (MFS) ≤15%. LV diastolic dysfunction was identified by any condition that differed from normal LV diastolic function, defined as an E/A ratio (Doppler transmitral flow) between 0.75 and 1.5 and E wave deceleration time >140 ms.

levels of all biomarkers, but the difference was statistically significant for only UACR and HbA_{1c}. Only NT-proBNP was significantly higher when LV ejection fraction was ≤50% (Table 1). The biomarkers showed poor accuracy for the detection of LV dysfunction (area under the receiver operating characteristic curves ≤0.58).

After 24 months of follow-up, incident LV dysfunction was found using echocardiography in 83 of 173 patients who did not have echocardiography-assessed LV dysfunction at baseline. None of the laboratory biomarkers centrally assayed at baseline predicted new occurrence of LV dysfunction. In logistic regression analyses, higher HbA_{1c} (median 6.7%) was the only independent predictor for the composite end point of all-cause mortality or hospitalization (142 events; odds ratio 1.30 [95% CI 1.05–1.62]; $P = 0.02$).

We report a lack of association between echocardiographic variables and laboratory biomarkers in a large population of type 2 diabetes patients without overt cardiac disease and mild alterations in LV function. The only laboratory marker found to predict 2-year outcomes in these patients was HbA_{1c}. Neither the other laboratory markers (NT-proBNP, hsCRP, and UACR) nor echocardiographic markers provided independent prognostic information. The role of HbA_{1c} as a guide for the appropriateness of treatment of patients with type 2 diabetes is supported by these findings.

Serge Masson, phd[1]
Roberto Latini, md[1]
Giovanni Cioffi, md[2]
Renato Urso, phd[3]
Tarcisio Vago, biold[4]
Donata Lucci, ms[3]
Gian Francesco Mureddu, md[5]
Luigi Tarantini, md[6]
Pompilio Faggiano, md[7]
Daniela Girfoglio, md[8]
Mario Velussi, md[9]
Aldo P. Maggioni, md[3]
Carlo B. Giorda, md[10]
Marco Comaschi, md[11]
on behalf of the DYDA Investigators

From the [1]Department of Cardiovascular Research, IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri," Milan, Italy; the [2]Echocardiography Laboratory, Villa Bianca Hospital, Trento, Italy; the [3]ANMCO Research Center, Florence, Italy; the [4]Laboratory of Endocrinology, Ospedale Luigi Sacco, Milan, Italy; the [5]Department of Cardiovascular Diseases, San Giovanni-Addolorata Hospital, Rome, Italy; the [6]Department of Cardiology, St. Martino Hospital, Azienda Sanitaria Locale n. 1, Belluno, Italy; the [7]Department of Cardiology, Spedali Civili, Brescia, Italy; the [8]Department of Clinical and Experimental Medicine, Federico II University, Naples, Italy; the [9]Department of Diabetology, Casa di Cura Pineta del Carso, Aurisina, Italy; the [10]Diabetes and Metabolism Unit, ASL Torino 5, Chieri, Italy; and the [11]Emergency Department, University Hospital San Martino, Genoa, Italy.

Corresponding author: Roberto Latini, roberto.latini@marionegri.it.

S.M. and R.L. contributed equally to the study.

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