Very long-term incidence of major cardiovascular events in patients with diabetes and chronic coronary syndrome: Data from the CICCOR registry

Incidencia a muy largo plazo de eventos cardiovasculares mayores en pacientes con diabetes y síndrome coronario crónico: datos del registro CICCOR

Diabetes and chronic coronary syndrome (CCS) are closely related: approximately one third of patients with CCS are diabetic,[1–3] and these patients have had a worse prognosis than patients without diabetes in prior studies.[1–3] However, information on long-term follow-up of this population is very limited in Spain. Our objective was to investigate very long-term prognosis in a cohort of patients with diabetes and CCS in day-to-day clinical practice.

The Cardiopatía Isquémica Crónica en CÓRdoba [Chronic Ischaemic Heart Disease in Córdoba] (CICCOR) registry was an observational, prospective, single-centre cohort study with the objective of researching CCS prognosis.[3] From 01/02/2000 to 31/01/2004, 1268 consecutive patients with CCS who attended two general cardiology appointments at a tertiary hospital, referred by primary care physicians, from the emergency department or for review following hospitalisation in cardiology or internal medicine were prospectively selected. All CICCOR registry patients with a diagnosis of diabetes mellitus at their baseline visit were selected for this analysis. The primary objective of the study was to investigate the very long-term incidence of major adverse cardiovascular events (MACEs) (combined event: infarction, stroke or cardiovascular death), that of each element of the primary objective, the incidence of admissions due to heart failure and overall mortality, as well as factors associated with MACE onset. The study was approved by the local Independent Ethics Committee, and the patients consented to inclusion in the study.

A total of 394 patients were included in the study. Table 1 shows the baseline characteristics of the series. None of the patients received dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide agonists at the baseline visit, as they were not on the market at that time in Spain. After a maximum follow-up of 17 years (median: 9 years; p25—75: 4–14 years), with just two patients lost to follow-up and 3517 patients per year of observation, 207 patients experienced a MACE. Of them, 55 patients had a stroke, 66 patients had an infarction and 165 patients died due to a cardiovascular cause. One hundred and one patients were admitted for heart failure; 238 patients died. The annual incidence of MACEs was 6.5 per 100 patient-years, with 1.64 corresponding to stroke, 1.97 to infarction, 3.12 to admission for heart failure, 4.69 to cardiovascular death and 6.77 to total mortality per 100 patient-years. The probability of survival free from each of these events after 12 years were 47%, 85%, 80%, 68%, 56% and 45%, respectively. In multivariate models, variables independently associated with MACEs were age (hazard ratio [HR] 1.06 [1.04–1.08], $p < 0.0005$), being a former smoker (HR 1.43 [1.02–1.99], $p = 0.04$) or an active smoker (HR 2.23 [1.16–4.30], $p = 0.02$), having angina in a functional class $\geq$ II (HR 1.57 [1.14–2.16], $p = 0.006$), baseline heart rate (HR 1.04 [1.00–1.08], $p = 0.04$) and treatment with diuretics (HR 1.71 [1.26–2.30], $p = 0.001$).

The major clinical trials that have studied new antidiabetic drugs in populations at high cardiovascular risk have generally found lower incidences of MACEs compared to our study.[4] Other observational studies[5,6] have shown rates of events that were lower than or similar to those of our study. Differences in baseline characteristics, history of cardiovascular disease, baseline kidney function, management of risk factors, rates of prior revascularisation and medical treatment might account for these differences. However, studies with a follow-up beyond five years are very limited. Hence, our study adds valuable information regarding these patients' very long-term course. This study also showed the impact on prognosis of simple clinical variables, which, though reported in general populations of patients with CCS,[1–3] had not been widely validated in the subgroup of patients with diabetes. The limitations of the study included the unavailability of information on type of diabetes, baseline glycosylated haemoglobin or other variables of prognostic interest, such as frailty, depression or social support; the impossibility of accurately describing changes in treatment over time, including the addition of drugs of prognostic interest such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide agonists; and the study's single-centre nature.

Finally, the main clinical implication of our study was the accurate picture it painted for the scientific community of the nature of the very long-term course of diabetic patients in the early decades of the 21 st century. The high rates of events found could represent an incentive to both optimise the management of classic cardiovascular risk factors and extend the use of new antidiabetic drugs which have demonstrated prognostic benefits.

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Table 1 Baseline characteristics of the sample and univariate predictors of major adverse cardiovascular events in follow-up.

Variable	Total N = 394	Major adverse CV events n = 207	No major adverse CV events n = 187	Hazard ratio (95% CI)	p
Age (years)	68.7 ± 8.3	69.9 ± 7.2	66.4 ± 9.8	1.05 (1.04–1.07)	<0.0005
Male sex, n (%)	241 (61.2)	121 (58.4)	120 (64.2)	0.90 (0.68–1.18)	0.45
Hypertension, n (%)	246 (62.6)	129 (62.3)	117 (62.9)	1.04 (0.78–1.37)	0.80
Active smoker, n (%)	21 (5.4)	13 (6.3)	8 (4.4)	1.21 (0.69–2.15)	0.51
Former smoker, n (%)	116 (29.9)	59 (28.6)	57 (31.3)	0.96 (0.71–1.30)	0.79
Dyslipidaemia, n (%)	294 (82.6)	160 (83.3)	134 (81.7)	0.90 (0.61–1.31)	0.57
Prior ACS, n (%)	332 (84.3)	176 (85)	154 (83.4)	1.18 (0.80–1.72)	0.40
Prior revasc., n (%)	172 (43.8)	91 (44)	81 (43.5)	0.88 (0.67–1.16)	0.36
Percutaneous revasc., n (%)	118 (30)	60 (29)	58 (31.2)	1.00 (0.98–1.00)	0.32
Surgical revasc., n (%)	61 (15.5)	33 (15.9)	28 (15.1)	0.93 (0.64–1.35)	0.69
Atrial fibrillation, n (%)	23 (5.9)	12 (5.8)	11 (6)	1.39 (0.77–2.49)	0.30
Prior CHF, n (%)	27 (6.9)	19 (9.2)	8 (4.3)	2.01 (1.25–3.23)	0.004
Angina FG ≥ II, n (%)	92 (23.4)	59 (28.5)	33 (17.6)	1.71 (1.27–2.32)	0.001
Baseline SBP (mmHg)	132.7 ± 15	133.2 ± 14.2	132.1 ± 16.5	1.00 (1.00–1.01)	0.45
Baseline DBP (mmHg)	74.5 ± 8.6	74.7 ± 8.7	74.6 ± 8.6	1.01 (0.99–1.02)	0.41
Baseline HR (bpm)	70.5 ± 12.3	71.2 ± 12.2	69 ± 11.4	1.01 (1.00–1.02)	0.02
Blood glucose (mg/dl)	165.1 ± 53.3	167.5 ± 58.3	161.8 ± 46.0	1.00 (0.99–1.01)	0.98
Baseline blood glucose <108 mg/dl, n (%)	14 (8.8)	10 (10.9)	4 (5.9)	1.76 (0.91–3.40)	0.09
Total cholesterol (mg/dl)	191.2 ± 38.7	195 ± 39.3	189.4 ± 37.9	1.00 (0.99–1.00)	0.51
HDL-C (mg/dl)	50.3 ± 12.3	50.8 ± 12.3	49.2 ± 12.7	1.01 (1.00–1.02)	0.12
LDL-C (mg/dl)	114.5 ± 32.4	114 ± 33.5	114.3 ± 31.3	0.99 (0.99–1.00)	0.77
LDL-C <70 mg/dl, n (%)	25 (8.2)	17 (10.1)	8 (5.9)	1.47 (0.89–2.43)	0.13
LDL-C <55 mg/dl, n (%)	3 (1)	3 (1.8)	0 (0)	6.96 (2.18–22.23)	0.001
Triglycerides (mg/dl)	135.3 ± 75.9	144.1 ± 86.7	126 ± 58.6	1.00 (1.00–1.00)	0.63
Creatinine (mg/dl)	1.1 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	1.78 (0.94–3.36)	0.1
GFR (ml/min)	63.7 ± 16.0	63.6 ± 16.1	63.9 ± 16.1	0.99 (0.98–1.00)	0.16
Haemoglobin (g/dl)	14.1 ± 2.7	14.2 ± 3.2	13.9 ± 1.7	0.98 (0.92–1.06)	0.64
Leukocytes ($10^3/\mu l$)	8.0 ± 1.7	7.9 ± 1.6	8.0 ± 1.9	1.02 (0.90–1.16)	0.79
Platelets ($10^3/\mu l$)	231.3 ± 75.0	239.1 ± 82.6	220.8 ± 62.4	1.00 (1.00–1.00)	0.10
Abnormal ECG, n (%)	268 (70.5)	139 (69.2)	129 (72.1)	1.13 (0.84–1.52)	0.43
Cardiomegaly n (%)	51 (14.3)	29 (15.2)	22 (13.3)	1.42 (0.95–2.11)	0.10
LVEF (%)	53.8 ± 14.8	53.7 ± 15.4	54 ± 14.1	1.00 (0.98–1.00)	0.32
Antiplatelet therapy, n (%)	359 (91.3)	187 (90.3)	172 (92.5)	0.67 (0.42–1.06)	0.10
Oral anticoagulation, n (%)	23 (5.9)	12 (5.8)	11 (5.9)	1.48 (0.83–2.66)	0.21
Beta blockers, n (%)	280 (71.1)	140 (67.6)	140 (74.9)	0.79 (0.59–1.05)	0.11
Statins, n (%)	258 (65.5)	137 (66.2)	121 (64.7)	0.77 (0.58–1.03)	0.08
Nitrates, n (%)	285 (72.5)	152 (73.4)	133 (71.5)	1.07 (0.78–1.45)	0.69
ACE inhibitors/ARBs, n (%)	240 (60.9)	128 (61.8)	112 (59.9)	1.03 (0.78–1.36)	0.86
Diuretics, n (%)	148 (37.7)	88 (42.5)	60 (32.3)	1.68 (1.27–2.22)	<0.0005

95% CI: 95% confidence interval; ACE inhibitors: angiotensin converting enzyme inhibitors; ACS: acute coronary syndrome; ARBs: angiotensin II receptor blockers; CHF: congestive heart failure; CV: cardiovascular; DBP: diastolic blood pressure; ECG: electrocardiogram; FG: functional grade; GFR: glomerular filtration rate; HDL-C: cholesterol bound to high-density lipoproteins; HR: heart rate; LDL-C: cholesterol bound to low-density lipoproteins; LVEF: left ventricular ejection fraction; revasc.: revascularisation; SBP: systolic blood pressure.

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Polyneuropathy as a neurological complication after sleeve gastrectomy

Polineuropatía como complicación neurológica tras gastrectomía tubular

Bariatric surgery (BS) is the most effective treatment for weight loss and maintenance thereof in patients with severe obesity, as well as management and/or remission of associated comorbidities. However, after BS, nutrient and vitamin deficiencies are common and can lead to neurological complications, which are usually secondary to deficiencies in B vitamins, vitamin E and/or copper.[1] Following restrictive procedures, such as sleeve gastrectomy (SG), neurological abnormalities are rare, but they can happen. The following are two illustrative case reports.

The first involved a 44-year-old woman with a BMI of 37.5 kg/m^2 who underwent SG at another hospital. After surgery, she presented daily vomiting, and after four months, she started to experience progressive weakness in her legs along with paraesthesia which rendered her unable to walk. She had not taken vitamin supplements, denied alcoholism and had lost 20 kg (17% of her baseline body weight). Physical examination revealed areflexia, weakness in her legs and pallhypaesthesia in her feet. Electromyography showed mild axonal sensorimotor polyneuropathy in her legs. Her cerebrospinal fluid (CSF) exhibited no abnormalities. Laboratory testing revealed deficiencies in calcidiol (24.1 nmol/L; normal >50), folate (<4.54 nmol/L; normal >8.8) and copper (65.2 μg/dl; normal >80); all other parameters and vitamins were normal. Intensive vitamin therapy was started based on the recommendations published by Yasawy et al.[2]: intramuscular vitamin B12 (1,000 μg daily for one week followed by 1,000 μg weekly), intravenous (IV) vitamin B1 (500 mg/day for three days followed by 100 mg/day), oral folic acid (5 mg/day) and copper sulphate (250 mg/day). She was referred to a centre specialising in rehabilitation and showed a partial recovery after 12 months (requiring crutches), and a full recovery after 24 months with no need for mobility aids.

The second case involved a 50-year-old woman with a BMI of 39 kg/m^2 who underwent SG at our hospital. After four months, she managed to lose 36.5 kg (37% of her baseline body weight), and two weeks prior to visiting the accident and emergency department, she had experienced repeated episodes of vomiting along with gradually worsening hypoaesthesia in her arms and legs as well as difficulty walking. She reported adherence to vitamin supplementation prescribed according to guidelines[3] (a daily multivitamin, calcifediol 16,000 IU every 15 days, calcium/cholecalciferol 1,000 mg/880 IU/day and folic acid 5 mg/day) and denied alcoholism. Physical examination revealed areflexia, hypoaesthesia in her arms and legs, slow gait with a wider base of support and dragging of the feet. Electromyography exhibited axonal sensorimotor polyneuropathy; cerebrospinal fluid testing showed no abnormalities. Laboratory testing revealed mild normocytic anaemia (Hb 116 g/L) and deficiencies in folate (<4.54 nmol/L), vitamin B1 (24 nmol/L; normal >78), vitamin B6 (25 nmol/L; normal >51), biotin (<100 ng/L; normal>100), vitamin C (<0.10 mg/dl; normal >0.4) and calcidiol (34 nmol/L); all other vitamins were normal (including vitamin B12: 265 pmol/L; normal >145). The patient was started on the same vitamin therapy regimen as in the previous case,[2] along with IV immunoglobulins. After 12 months, she showed a partial recovery, and after 24 months, she showed a full recovery, with no need for mobility aids.

The incidence of neurological complications following BS ranges from 0.7% to 5%, depending on the series.[4] Most of them develop after malabsorptive procedures, but they have also been reported after restrictive procedures. Their onset is usually 3–20 months after surgery, and the main risk factors are prolonged vomiting, alcoholism, lack of adherence to vitamin supplementation and large amount of weight loss. The most common are those associated with deficiencies in some B vitamins (B1, B9 and B12); however, they have also been reported in relation to deficiencies in vitamin E, copper, pyridoxine and niacin.[1] Peripheral neuropathy is uncommon, and Guillain–Barré syndrome-like peripheral neuropathy is even less common, with hardly any cases reported in the literature[2,5–7] (Table 1).

When neurological signs and symptoms are present following SG, it is essential to rule out deficiencies in vitamin B12, vitamin B1, vitamin E, copper and folic acid primarily. Up to 18% of patients who undergo SG may present vitamin B12 deficiency.[8] This deficiency has been linked to posterior