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Original Article

Comorbidity assessment for mortality risk stratification in elderly patients with acute coronary syndrome

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ABSTRACT

Background: The Charlson's is the most used comorbidity index. It comprises 19 comorbidities, some of which are infrequent in elderly patients with acute coronary syndrome (ACS), while some others are manifestations of cardiac disease rather than comorbidities. Our goal was to simplify comorbidity assessment in elderly non-ST-segment elevation ACS patients.

Methods: The study group consisted of 1 training (n = 920, 76 ± 7 years) and 1 testing (n = 532; 84 ± 4 years) cohorts. The end-point was all-cause mortality at 1-year follow-up. Comorbidities were assessed selecting those medical disorders other than cardiac disease that were independently associated with mortality by multivariable analysis.

Results: A total of 130 (14%) patients died in the training cohort. Six comorbidities were predictive: renal failure, anemia, diabetes, peripheral artery disease, cerebrovascular disease and chronic lung disease. The increase in the number of comorbidities yielded a gradient of risk on top of well-known clinical predictors: ≥3 comorbidities (27% mortality, HR = 1.90, 95% CI 1.20–3.03, p = .006); 2 comorbidities (16% mortality, HR = 1.29, 95% CI 0.81–2.04, p = .30); and 0–1 comorbidities (7.6% mortality, reference category). The discrimination accuracy (C-statistic = 0.80) and calibration (Hosmer-Lemeshow test, p = .20) of the predictive model using the 6 comorbidities was comparable to the predictive model using the Charlson index (C-statistic = 0.80; Hosmer-Lemeshow test, p = .70). Similar results were reproduced in the testing cohort (≥3 comorbidities: 24% mortality, HR = 2.37, 95% CI 1.25–4.49, p = .008; 2 comorbidities: 14% mortality, HR = 1.59, 95% CI 0.82–3.07, p = .20; 0–1 comorbidities: 7.5% reference category).

Conclusion: A simplified comorbidity assessment comprising 6 comorbidities provides useful risk stratification in elderly patients with ACS.

1. Introduction

Comorbidities are highly prevalent in elderly patients with acute coronary syndrome (ACS) [1–7]. The fact that they may confound prognosis evaluation of the primary illness is a matter of concern [8]. Several comorbidity indices have been introduced for prognosis assessment, among which the Charlson index is the most commonly used [9]. However, it seems unlikely that a single tool, based on a historical

Abbreviations: ACS, Acute coronary syndrome

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cohort of medical patients derived in 1984, is equally effective in a wide spectrum of primary diseases nowadays. Indeed, a specific comorbidity index derived from kidney transplant recipients showed greater accuracy for mortality prediction in these patients [10]. Cardiac-specific and simpler indices have been developed in stable coronary artery disease and ACS to facilitate comorbidity evaluation [3,11]. Nonetheless, they were not derived from elderly populations or have included factors (such as myocardial infarction and congestive heart failure) that represent the underlying coronary disease rather than comorbidities. Furthermore, cardiac treatments can potentially modify the prognosis dependent on the cardiac conditions but the optimization of ACS patients also requires the treatment of comorbidities. Consequently, delineating the prognosis inherent to comorbidities is of paramount importance for decision-making, particularly in elderly patients. The aim of this study was to elucidate the most common non-cardiac diseases with prognosis impact on mortality in elderly patients with ACS. The main goal was to simplify comorbidity assessment in these patients.

2. Methods

2.1. Patient population

The study group consisted of training and testing cohorts. The training cohort was an individual patient data pooled analysis from 2 cohorts of elderly (≥65 years old) patients admitted for non-ST segment elevation ACS at the Cardiology Department of the University Clinic Hospital in Valencia, Spain. A total of 920 patients were included, 650 from the first cohort (from October 1, 2002, to October1, 2008) [3], and 270 from the second cohort (from October 1, 2010, to February 1, 2012) [5,12]. A detailed description of the cohorts can be found in previous publications [3,5,12]. The study was reviewed and approved by the Ethics Committee of the University Clinic Hospital in Valencia.

A number of variables were collected during hospitalization from clinical assessment (age, gender, coronary risk factors, prior history of ischemic heart disease, prior hospitalization for heart failure, and admission Killip class), electrocardiograms (ST-segment depression), routine blood tests (troponin levels, admission hemoglobin level, and glomerular filtration rate), and echocardiograms (left ventricular ejection fraction). The primary end point was all-cause mortality at 1-year follow-up. All patients but 9 completed the follow-up.

The LONGEVO-SCA *("Impacto de la fragiLidad y Otros síndromes GEriátricos en el manejo y pronóstico Vital del ancianO con Síndrome Coronario Agudo sin elevación de segmento ST")* registry was used as testing cohort. This is a prospective, multicenter observational study conducted at 44 Spanish hospitals, which enrolled 532 consecutive patients, between March 2016 and September 2016, aged 80 years or older admitted for non-ST-segment elevation ACS (mean age = 84.3 ± 4.0 years) [7]. The primary endpoint was all-cause mortality at 6 months' follow-up.

The Charlson index was measured in the training as well as in the testing cohort.

2.2. Comorbidity definition

Comorbidities were defined as medical disorders other than cardiac disease. Explicitly, from the Charlson index, prior myocardial infarction or heart failure were not considered as comorbidities but as covariates for adjustment. Therefore, the following factors of the Charlson index were considered: renal disease, diabetes (either with or without end organ damage), peripheral artery disease, cerebrovascular disease (either with or without permanent neurological deficit), chronic lung disease, dementia, malignancy (either with or without metastases), liver disease (mild or severe), peptic ulcer and any rheumatic disease. Acquired immune deficiency syndrome was not considered because of its very low prevalence among acute cardiac patients (no patients in our series). Finally, anemia, not included in the Charlson index, was added as comorbidity because of its significant prevalence and prognostic implications in ACS [13].

2.3. Statistical analysis

Continuous variables were expressed as mean values ± standard deviation and compared with the unpaired *t*-test. Categorical variables were presented as absolute values and percentages, and compared with the chi-square test. Association of each individual comorbidity (renal failure diabetes, peripheral artery disease, cerebrovascular disease, chronic lung disease, dementia, any cancer, liver disease, peptic ulcer, any rheumatic disease, and anemia) with total mortality was estimated using a univariate Cox regression model, calculating the hazard ratio (HR), 95% confidence intervals (CI) and statistical significance (p). Renal failure was defined as glomerular filtration rate (< 60 mL/min/1.73 m^2). Anemia was defined according to the World Health Organization criteria (hemoglobin < 13 g/dL in men or < 12 g/dL in women). Since hemoglobin level < 11 g/dl was the best cutoff for predicting clinical outcomes in ACS in a previous study [13], we used the following categories for anemia: Normal (hemoglobin ≥13 g/dL in men or ≥ 12 g/dL in women), mild anemia (hemoglobin < 13 g/dL in men or < 12 g/dL in women, but ≥11 g/dL), and severe anemia (hemoglobin < 11 g/d). Next, those comorbidities that achieved significant level of $p < .25$ in the univariate analysis, were selected for testing a multivariable Cox model (backward elimination). Six comorbidities were significantly ($p < .05$) associated with mortality in the multivariable model: Renal failure, severe anemia, diabetes mellitus, peripheral artery disease, cerebrovascular disease and chronic lung disease.

A comorbidity variable was created according to the number of the 6 comorbidities present, and its predictive power was tested after full adjustment for clinical data (Cox regression, backward method). Those clinical variables associated ($p < .25$) with mortality in the univariate analysis were chose for the multivariable model. The discrimination accuracy (C-statistic) and calibration (Hosmer-Lemeshow chi-square statistics for goodness of fit) of the model were estimated and the same was done for a model using the Charlson index instead of the 6 comorbidities. In addition, a sensitive analysis of the association between in-hospital revascularization at the index episode and 1-year mortality according to the comorbidity status was carried out. To this effect, 2 groups of patients were considered, ≥3 (n = 187) and < 3 (n = 733) comorbidities. Finally, the predictive performance of the 6 comorbidities was analysed in the testing cohort. Statistical analysis was performed using SPSS version 20.0 software (SPSS, Inc., Chicago, IL).

3. Results

3.1. Baseline patient characteristics of the training cohort

The patient population's complete characteristics including the frequency of the individual comorbidities are detailed in Table 1. Mean Charlson index was 2.13 ± 1.94 points. A total of 130 patients (14%) died during the 1-year follow-up.

3.2. Comorbidity assessment

Table 2 shows the association of each comorbidity with mortality. Six comorbidities were independently associated with mortality in the multivariable analysis: Renal failure, severe anemia, diabetes mellitus, cerebrovascular disease, peripheral artery disease, and chronic lung disease. Fig. 1 depicts mortality distribution depending on the number of these 6 comorbidities present. Mortality stepwise increased with higher number of comorbidities ($p = .0001$).

The number of comorbidities maintained the predictive value along with well-known clinical predictors, such as prior admission for heart

Table 1
Baseline characteristics of the patient population.

	Training cohort (n = 920)	Testing cohort (n = 532)
Men	533 (58%)	328 (60%)
Age (years)	76.4 ± 7.0	84.0 ± 4.0
Smoking	92 (10%)	174 (32%)
Hypertension	700 (76%)	457 (84%)
Hypercholesterolemia	470 (51%)	340 (62%)
Prior myocardial infarction	285 (31%)	186 (34%)
Prior coronary angioplasty	108 (12%)	153 (28%)
Prior coronary surgery	81 (8.8%)	51 (9.4%)
Killip ≥ 2	213 (22%)	151 (28%)
Prior admission for heart failure	111 (12%)	94 (7%)
ST-segment depression	384 (42%)	231 (42%)
Troponin elevation	695 (76%)	450 (83%)
Left ventricular ejection fraction (%)	57 ± 13	53 ± 12%
Invasive management	634 (69%)	417 (77%)
In-hospital revascularization	356 (39%)	292 (54%)
Follow-up	1 year	6 months
All-cause mortality	130 (14%)	63 (12%)
Comorbidities		
Renal failure[a]	492 (54%)	213 (40%)
Mild anemia[b]	170 (19%)	141 (26%)
Severe anemia[b]	121 (13%)	91 (17%)
Diabetes	415 (45%)	212 (39%)
Cerebrovascular disease	100 (11%)	80 (15%)
Peripheral artery disease	95 (10%)	72 (13%)
Dementia	46 (5%)	25 (4.6%)
Chronic lung disease	109 (12%)	80 (15%)
Malignancy	77 (8.4%)	78 (15%)
Rheumatic disease	59 (6.4%)	15 (2.8%)
Liver disease (mild or severe)	10 (1.1%)	7 (1.3%)
Peptic ulcer	37 (4%)	34 (6.3%)
Charlson index (points)	2.13 ± 1.94	2.39 ± 1.86

[a] Glomerular filtration rate < 60 mL/min/1.73 m^2.
[b] Mild anemia (hemoglobin < 13 g/dL in men or < 12 g/dL in women, and ≥ 11 g/dL) and severe anemia (hemoglobin < 11 g/dL).

Table 2
Association of each comorbidity with mortality by univariable and multivariable Cox regression analysis.

	Univariable			Multivariable		
Comorbidities	HR	95% CI	p	HR	95% CI	p
Renal failure	2.74	1.85–4.07	0.0001	2.14	1.42–3.22	0.0001
Mild anemia[a]	1.3	0.82–2.05	0.25			0.80
Severe anemia[a]	2.75	1.83–2.05	0.0001	1.99	1.30–3.04	0.002
Diabetes	1.28	0.93–1.74	0.13	1.55	1.08–2.21	0.02
Cerebrovascular disease	1.66	1.04–2.65	0.04	1.60	1.00–2.56	0.05
Peripheral artery disease	2.53	1.66–3.86	0.0001	1.81	1.16–2.80	0.008
Chronic lung disease	2.18	1.43–3.31	0.0001	1.96	1.27–3.00	0.002
Dementia	2.06	1.14–3.72	0.02			0.25
Malignancy	1.51	0.88–2.58	0.20			0.50
Rheumatic disease	0.84	0.39–1.79	0.70			
Liver disease	1.51	0.37–6.09	0.60			
Peptic ulcer	0.75	0.28–2.04	0.60			

Abbreviations: HR = Hazard ratio. CI = Confidence interval. P = Statistical significance.
[a] Reference group with normal hemoglobin (≥ 13 g/dL in men or ≥ 12 g/dL in women).

failure, Killip class ≥ 2 at admission, ST-segment depression, lefyt ventricular ejection fraction and in-hospital revascularization. According to the distribution of mortality across the number of comorbidities, 3 categories of risk were distinguished: ≥ 3 comorbidities (27% all cause-mortality; HR = 1.90, 95% CI 1.20 to 3.03, p = .006); 2 comorbidities (16% all-cause mortality; HR = 1.29, 95% CI 0.81 to 2.04, p = .30); and 0–1 comorbidities (7.6% all-cause mortality; reference category) (Fig. 2, Table 3). The predictive model using the

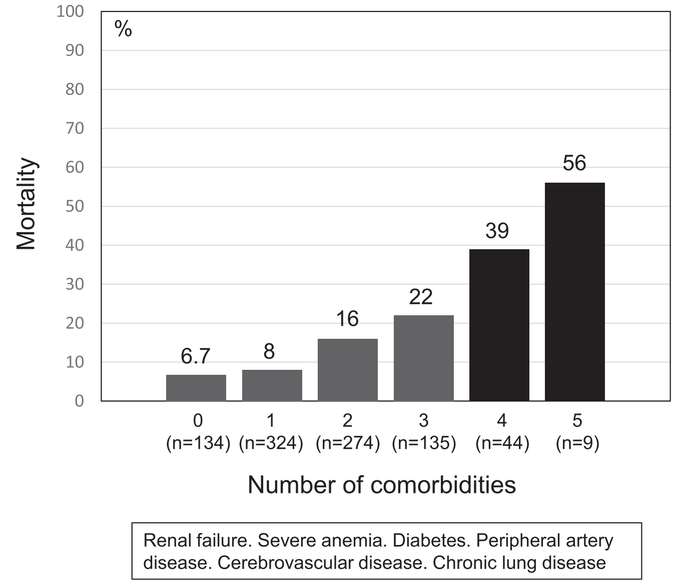

Fig. 1. Mortality distribution depending on the number of the 6 comorbidities present. Mortality stepwise increased with higher number of comorbidities (p = .0001). X-axis: Number of comorbidities (number of patients in brackets). Y-axis: Percentage of mortality.

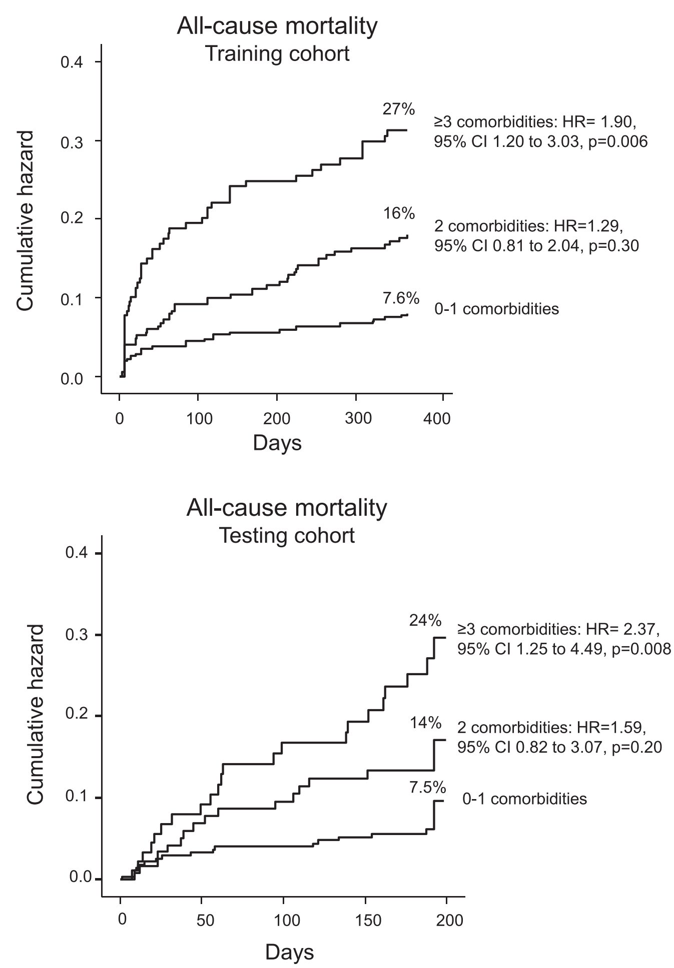

Fig. 2. Kaplan-Meier curves for all-cause mortality according to the number of comorbidities in the training (top) and testing (bottom) cohorts. Hazard ratios adjusted for clinical predictors. Abbreviations: HR = Hazard ratio. CI = Confidence interval. P = statistical significance.

Table 3
Predictive model for all-cause mortality taking into account clinical variables and the number of comorbidities.

	Hazard ratio	95% CI	p
Prior admission for heart failure	1.53	1.02–2.31	0.04
Admission Killip class ≥2	2.52	1.69–3.74	0.0001
ST-segment depression	1.65	1.16–2.34	0.005
Left ventricular ejection fraction (per 5%)	0.88	0.83–0.94	0.0001
Revascularization at the index episode	0.38	0.24–0.61	0.0001
Number of comorbidities[a]			
≥3 comorbidities	1.91	1.20–3.03	0.006
2 comorbidities	1.29	0.81–2.04	0.30

Non-predictive clinical variables: Age, gender, smoking, hypertension, hypercholesterolemia, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary bypass graft, troponin elevation.
[a] Reference subgroup = 0–1 comorbidities.

number of comorbidities showed good calibration (p for Hosmer-Lemeshow test = 0.20) and provided similar discrimination accuracy (C-statistic = 0.80) to the model using the Charlson index (C-statistic = 0.80; p for Hosmer-Lemeshow test = 0.70).

The level of comorbidity was lower in patients revascularized during the hospitalization for the index episode (number of comorbidities: 1.4 ± 1.1 vs 1.8 ± 1.2, p = .0001). In the sensitive analysis, in-hospital revascularization reduced mortality in both, the group of patients with ≥3 comorbidities (12.5% vs 32.8%; HR = 0.38, 95% CI 0.17 to 0.85, p = .02) and < 3 comorbidities (5% vs 15%; HR = 0.36, 95% CI 0.20 to 0.63, p = .0001). Although in absolute terms, the magnitude of the mortality reduction was greater in the most comorbid patients (20.3% vs 10%), the interaction in-hospital revascularization- ≥3 comorbidities was not significant (p = .60).

3.3. Testing cohort

Table 1 shows the patient characteristics, comorbidities and outcomes in the testing cohort. Categorization according to comorbidities appropriately reproduced the gradient of mortality risk in this cohort (≥3 comorbidities: 24% all-cause mortality, HR = 2.37, 95% CI 1.25 to 4.49, p = .008; 2 comorbidities: 14% all-cause mortality, HR = 1.59, 95% CI 0.82 to 3.07, p = .20; 0–1 comorbidities: 7.5% all-cause mortality, reference subgroup) (Fig. 2). Likewise, the calibration and discrimination accuracy of the predictive model using the number of comorbidities (p for Hosmer-Lemeshow test = 0.20, C-statistic = 0.79) were comparable to that using the Charlson index (p for Hosmer-Lemeshow test = 0.60, C-statistic = 0.81).

4. Discussion

This study identified 6 comorbidities with predictive value for mortality in elderly patients with ACS: Renal failure, severe anemia, diabetes, cerebrovascular disease, peripheral artery disease and chronic lung disease. The increase in the number of these comorbidities yielded a gradient of mortality risk on top of well-known clinical predictors. The assessment of the 6 comorbidites is simpler and performed as well as the Charlson index for prognosis evaluation. In particular, the presence of 3 or more comorbidities portended a high mortality risk. This approach might conceivably be relevant for personalized diagnostic and therapeutic management of elderly patients with ACS.

4.1. Comorbidities and prognosis after acute coronary syndromes

The age of patients hospitalized with ACS is rising in parallel with the longer life expectancy. Therefore, assessing geriatric conditions is acquiring increased importance for decision making [14]. However, most currently used risk scores do not take comorbidities into account [15]. Some studies have demonstrated that comorbidities are independent predictors of mortality and improve the accuracy of risk predictive models in ACS [1–7,12,16,17]. Our study confirms that the comorbidity evaluation adds independent prognosis information to well-known clinical predictors in ACS.

4.2. Limitations of the Charlson index

The Charlson's is the most commonly used comorbidity index [9]. Recently, Rashid et al. published a meta-analysis, including 5 studies statistically pooled, evaluating the impact of comorbidities in patients admitted with acute coronary syndrome [18–23]. This meta-analysis shows that increasing co-morbid burden as defined by Charlson index is associated with a significant increase in risk of mortality. Some limitations of the Charlson index, however, deserve to be underscored: 1) It includes cardiac factors (myocardial infarction or heart failure) that conceptually should not be considered comorbidities in patients with ACS. 2) The index was derived from a cohort of medical patients in 1984 quite different to populations nowadays. Its calculation has some complexity since it contains 19 items according to the prevalence of comorbidities in the original population The Charlson index was reevaluated and weighs reassigned for patients admitted in a General Hospital in 2004 and for patients with stable ischemic heart disease [24]. Yet the prevalence of the comorbidities and their prognostic weight could be different in elderly patients with ACS currently seen in a Cardiology Department.

4.3. Individual comorbidities

The individual comorbidities associated with mortality in our cohort of elderly patients with non-STE-elevation ACS were renal failure, diabetes, cerebrovascular disease, peripheral artery disease, chronic lung disease and severe anemia. Renal failure was associated with mortality in non-STE-elevation ACS in previous studies [25] Diabetes is a well-known predictor of mortality not only because of cardiovascular disease but also because of several other associated disorders [26]. Cerebrovascular disease and peripheral artery disease, although might be considered as disease staging of underlying atherosclerosis [4], are actually diseases in organs other than the heart. They were predictive in our study despite not being so in a population admitted to a General Hospital [24], pointing to the limitations of using a single comorbidity score for a wide variety of patients suffering from different primary diseases. Chronic lung disease conveys poor prognosis in ACS, which was in part attributed to the underuse of guideline recommended treatments [27].

Anemia is a quiet prevalent and strong predictor of mortality in ACS not included in the Charlson index [13]. In a meta-analysis including 27 studies and involving 233,144 patients with ACS, anemia at admission was significantly associated with an increased risk of 1-year mortality [28]. The most used threshold for anemia is the definition of the World Health Organization. As a whole, hemoglobin levels are lower in older people [29]. Since hemoglobin below 11 g/dL was also a significant threshold in clinical trials on non-ST-elevation ACS, we also tested the 11 g/dL threshold [13]. Indeed, the mortality risk increased remarkably when hemoglobin fell below 11 g/dL, as was also reported in other studies [13].

4.4. Clinical implications

Current guidelines recommend routine invasive management early after admission for non-ST-elevation ACS. However, this policy tends to be underused in real clinical practice in comorbid patients [3]. It is possible that invasive management cannot modify the worse prognosis associated with comorbidities. The After Eighty trial demonstrated the benefit of routine invasive management in patients older than 80 years [30]. Comorbid patients, however, are underrepresented in the trial. Another randomized trial specifically targeted at non-ST-segment elevation ACS with comorbidities, found no differences between routine invasive management and an initially conservative approach alongside watchful waiting for crossover in the case of clinical instability [31]. Further studies are needed to elucidate the best management of elderly patients with geriatric conditions and non-ST-elevation ACS [32–34]. In another scenario, such as percutaneous coronary intervention of ST-segment elevation myocardial infarction in multi-vessel disease, multi-vessel revascularization improved and comorbidities worsen outcomes [35].

4.5. Strengths and limitations

The main strength of the study is that all the predictive variables were easily and directly obtained from the patients and not from electronic databases.

The main limitation is that the sample size was smaller and the follow-up period a bit shorter in the testing cohort; however, the results followed the same pattern as in the training cohort. In any case, this proposal of a simplified comorbidity assessment in elderly patients with ACS needs to be validated in larger cohorts. On the other hand, the study has limited power for subgroup analysis, in particular to elucidate the potential interaction between comorbidities and revascularization for outcomes.

4.6. Conclusions

A simplified comorbidity assessment based on 6 extra-cardiac diseases affords risk classification of patients according to their comorbidities in non-ST- segment elevation ACS in the elderly. This information may be useful for decision making in the management of elderly patients with ACS.

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Conflict of interest statement

Dr. Sanchis reports grants from Biotronik, Prosmedica and Bayer outside the submitted work. Dr. Núñez reports personal fees from Novartis, Vifor, Rovi, Boehringer Ingelheim and Novo Nordisk, outside the submitted work. Dr. Bueno reports grants and personal fees from ASTRA ZENECA, DAICHII-SANKYO, ELI-LILLY, BAYER, and SANOFI, during the conduct of the study; personal fees from NOVARTIS, BMS-PFIZER and SERVIER, outside the submitted work.

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