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Heart failure in women and men during acute coronary syndrome and long-term cardiovascular mortality (the ABC-3* Study on Heart Disease) (*Adria, Bassano, Conegliano, and Padova Hospitals)

Giuseppe Berton [a,*], Rocco Cordiano [b], Fiorella Cavuto [c], Francesco Bagato [b], Marco Pellegrinet [d], Arianna Cati [a]

[a] Department of Cardiology, Conegliano General Hospital, Conegliano, Italy
[b] Department of Internal Medicine and Cardiology, Adria General Hospital, Adria, Italy
[c] Department of Cardiology, Bassano del Grappa General Hospital, Bassano del Grappa, Italy
[d] Department of Internal Medicine and Cardiology, Udine University Hospital, Udine, Italy

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ABSTRACT

Aims: We investigated the gender-based differences in the association between heart failure (HF) during acute coronary syndrome (ACS) and post-discharge, long-term cardiovascular (CV) mortality.
Methods and results: The present study included 557 patients enrolled in three intensive coronary care units and discharged alive. HF during ACS was evaluated by Killip class and left ventricular ejection fraction (LVEF). Interaction between gender and HF after 15 years of follow up was studied using Cox models including a formal interaction term. Median age was 67 (interquartile range [IQR], 59–75) years, 29% were females, 37% had non-ST elevation myocardial infarction and 32% Killip class > 1, and median LVEF was 53% (IQR 46–61). All but five patients were followed up to 15 years, representing 5332 person-years. Of these, 40.2% died of CV-related causes. Crude CV mortality rate was higher among women (52.2%) than men (35.3%; $P < 0.0001$). At a univariable level, a negative interaction between female gender and Killip class for CV mortality was found [hazard ratio (HR) = 0.51 (0.34–0.77), $P = 0.002$]. In five multivariable models after controlling for age, main CV risk factors, clinical features, post-discharge medical treatment, and mechanical coronary reperfusion, the interaction was significant across all models [HR = 0.63 (0.42–0.95), $P = 0.02$ in the fully adjusted model]. LVEF showed no significant hazard associated with female gender on univariable analysis [HR = 1.4 (0.9–0.2.0), $P = 0.11$] but did so in all adjusted models [HR = 1.7 (1.2–2.5), $P = 0.005$ in the fully adjusted model].
Conclusion: Gender is a consistent, independent effect modifier in the association between HF and long-term CV mortality after ACS.

1. Introduction

Natural history studies have suggested differences in survival between men and women in a broad spectrum of heart failure (HF) severity [1–4]. The Framingham Heart Study found that the prognosis for women was better than for men after the onset of signs of HF [1,2]. In patients with acute coronary syndrome (ACS), women have a worse prognosis than men, but the adverse course was attributed to their baseline characteristics and not to gender per se [5,6]. Indeed, it is well established that the presence of HF during ACS is one of the most important clinical manifestations leading to adverse outcomes [6,7]. Nonetheless, the relationship between gender and HF for adverse prognosis after ACS has not been thoroughly examined, especially in the long term. Studies have focused on gender differences for adverse outcomes associated with age, type of ACS, or treatment [8–11]. Furthermore, a recent overview of the current understanding of possible gender differences in cardiovascular (CV) risk factors, therapy, and prognosis of ACS reported no data on the relationship between gender and HF [12]. Our aim was to investigate prospectively the gender-based differences in the association between HF during ACS and post-discharge, long-term CV mortality.

2. Methods

2.1. Patients

The Adria, Bassano, Conegliano, and Padova Hospital Study on Heart Disease (the ABC Study on ACS) is an ongoing, prospective investigation designed to reflect, as closely as possible, an unbiased population of patients with ACS. The sample includes Caucasian patients with definite

* Corresponding author at: Cardiology Department, Conegliano General Hospital, Via Brigata Bisagno, 31015 Conegliano, (TV), Italy.
E-mail address: giube.s@alice.it (G. Berton).

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ACS (ST elevation myocardial infarction [STEMI], non-ST elevation myocardial infarction [NSTEMI], and unstable angina [UA]), admitted to the intensive care units of Adria, Bassano, and Conegliano hospitals between June 21, 1995, and January 19, 1998. The original aim of the ABC study was to follow the natural, long-term history of the patients and to evaluate the prognostic value of a number of clinical variables. The criteria for the diagnosis of ACS included the clinical presentation, electrocardiogram (ECG) findings, and the identification of serum biochemical markers of necrosis. Specifically, acute myocardial infarction was defined as the typical rise and gradual decline of creatine kinase MB expression, accompanied by at least one of the following conditions: ischemic symptoms, development of pathologic ECG Q waves, and ECG changes indicative of ischemia (i.e., ST segment elevation or depression). Myocardial infarction was also classified as type 1 and type 2, according to the third universal definition of myocardial infarction [13]. UA is described as the occurrence of one or more episodes of angina at rest within the preceding 48 h, corresponding to class III of the Braunwald classification, with ECG changes indicative of ischemia [14].

A total of 778 eligible patients were considered upon admission. Of these, 47 patients had diseases other than coronary artery disease (CAD), and 53 patients had CAD, but not ACS; these patients were excluded from the study. Seventy-nine patients were excluded from the study for concomitant conditions potentially affecting the investigated variables, as detailed elsewhere [7]. Forty-two of the enrolled patients died during the index hospitalization and were excluded from the present analysis. Hence, the post-discharge follow-up study included 557 patients. Each patient received an anonymous code, and no personal data or identifiers were included in the baseline or follow-up database. Written informed consent was obtained from all enrolled patients, and the study was approved through the hospital ethics committee.

2.2. Measurements

At enrollment, a thorough patient history from medical records and patient interviews was collected. All baseline clinical and laboratory data reported in the present study were obtained during the first 7 days of hospitalization in the intensive coronary care unit. Details of variables accrued have been published elsewhere [7,15]. We investigated the presence and degree of HF during ACS by means of Killip class and left ventricular ejection fraction (LVEF) [16,17]. Killip classification was recorded as follows: class 1, no signs of HF; class 2, pulmonary rales; and class 3, pulmonary edema or cardiogenic shock (Killip classes 3 and 4) [15]. The highest class observed during the first 7 days of the hospital stay was used in the present analysis. LVEF was assessed using two-dimensional echocardiography according to Simpson's method [17]. The LVEF was missing for 81 patients who underwent echocardiography after discharge from the intensive care units or who had technically inadequate echocardiographic images. Two physicians, with no knowledge of the patient clinical data, examined the records.

2.3. Follow-up and outcomes

At 1, 3, 5, 7, 10, 12, and 15 years after recruitment, each patient underwent a clinical check-up. At each recruitment hospital, two cardiologists took care to follow the surviving cohort through the 15 years of follow-up. The pre-specified primary endpoint of the present study was to determine the 15-year CV mortality. Two researchers, unaware of baseline patient data, examined the modes of death. CV mortality included: CAD and/or HF progression; sudden death, defined as witnessed, out-of-hospital death within 1 h after the onset of acute symptoms or unwitnessed, unexpected death (e.g., during sleep) in patients within the 24 h prior to the onset of symptoms; and other CV causes [7,18]. All data regarding the events were obtained from a scheduled check-up, public administration and hospital records, family doctors, postmortem examinations, and death certificates. Reports were also obtained regarding the medications administered during the index hospitalization and follow-up treatments. If a patient underwent heart transplantation, that patient was censored at the time of transplantation.

2.4. Statistical analysis

Unpaired Student's t-test and Pearson chi-square (χ^2) test were used for measured and categorical variables, respectively. Log transformations were used to correct for positive-skewed distributions, as appropriate. In survival analysis, LVEF was analyzed as tertiles of increasing values. Cox proportional hazard regression analysis was used to describe the influence of the variables on mortality during follow-up [19]. If a patient dropped out before completing 15 years of follow up, that patient's data were censored at that time. Scaled Schoenfeld residuals were used to test the proportionality assumption with a 95% confidence interval (CI) [20]. The interaction between gender and HF was studied first by means of odds ratios (ORs) and the Mantel–Haenszel test of homogeneity (with $P < 0.05$ indicating dis-homogeneity of the OR). Then, Cox survival regressions, including a formal interaction term between gender and HF and adjusting for main clinical variables and main treatments, were used. The risk estimate was quantified as the hazard ratio (HR). To show graphically gender HR ratios for CV mortality across increasing degrees of Killip class and tertiles of LVEF, marginal analysis was used.

The baseline characteristics were summarized using medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables. Unless otherwise indicated, two-tailed P values <0.05 were deemed significant. The statistical analyses were performed using STATA 13.

3. Results

3.1. Baseline characteristics

A total of 28.9% of the 557 patients in the sample were women. Table 1 summarizes the main clinical characteristics by gender. Overall, women were older than men and more likely to have hypertension and diabetes mellitus and a history of angina and higher systolic blood pressure values and total cholesterol at enrollment (Table 1). They had lower body mass index and were less likely ever to have smoked. Women had more frequent and more severe signs of HF and a lower heart rate, estimated glomerular filtration rate, and CK-MB peak than men while LVEF was similar between men and women (Table 1). Main treatments differed by gender, including thrombolytic treatment at enrollment and mechanical revascularization during follow-up, which were all less frequently used for women except for angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, which were used more in women.

3.2. Death rate by gender and OR by Killip class and LVEF

All patients included in this study underwent 15-year observation or time to death, except for five who dropped out (two patients withdrew consent and one patient moved overseas) and two who underwent heart transplantation. The entire sample represented 5332 person-years of follow-up, and 224 patients (40.2%) died of a CV-related cause. Crude mortality rate was higher among women (52.2%) than among men (35.3%; $P < 0.0001$). Overall, at the univariable level, both Killip class and LVEF (increasing and decreasing risk respectively) ORs were associated with outcome (Table 2). Indeed, among male patients, OR was much higher than among females, and the Mantel–Haenszel test of homogeneity showed significant differences. This result indicates a negative interaction between gender and degree of Killip class for CV mortality, i.e., the higher the degree of Killip class, the lower the mortality risk for the women compared to the men. The same univariable

Table 1
Baseline characteristics of the patients by gender.

Variable name	Overall sample (N = 557)	Male (N = 396)	Female (N = 161)	*P* value
Age (years)	67 (58–74)	64 (55–71)	73 (67–79)	<0.0001
Current smoking	38	46	17	<0.0001
Hypertension	46	39	65	<0.0001
Diabetes mellitus	21	18	31	<0.0001
Body mass index (kg/m^2)	26 (24–28)	26 (24–28)	25 (22–27)	<0.0001
History of angina	25	22	32	0.02
Previous myocardial infarction	24	24	24	0.82
Pre-hospital time delay (n = 465)	180 (120–510)	180 (120–480)	240 (120–660)	0.07[a]
ST elevation ACS	61	64	55	0.06
Type 2 myocardial infarction	8.6	7.1	12.4	0.04
Total cholesterol (mmol/L)	208 (179–243)	205 (177–238)	220 (188–247)	0.04
Systolic blood pressure (mm Hg)	121 (108–133)	119 (108–131)	124 (111–137)	0.004
Diastolic blood pressure (mm Hg)	77 (69–83)	77 (68–83)	77 (69–83)	0.82
Heart rate (beats/min)	70 (60–78)	68 (60–75)	75 (66–84)	<0.0001
CK MB peak (U/L)[a]	103 (43–207)	107 (47–221)	74 (35–175)	0.009[a]
Killip class[b]				<0.0001
1 (no heart failure)	68	73	53	
2 (heart failure)	28	23	38	
3 (pulmonary edema/cardiogenic shock)	5	3	8	
LVEF (%) (n = 476)	53 (46–61)	53 (46–60)	52 (46–62)	0.87
eGFR (mL/s × 1.73 m^2)[a]	73 (61–87)	76 (64–88)	65 (56–81)	<0.0001[a]
Main treatment				
Thrombolysis (at enrollment)	35	38	28	0.02
ß-receptor blocker	51	55	39	0.001
ACE-inhibitor/angiotensin II receptor blocker	73	71	78	0.05
Antiplatelet	90	91	85	0.02
Lipid-lowering drug	32	36	22	0.001
PTCA (during follow-up)	19	21	13	0.03
CABG (during follow-up)	19	22	12	0.006

Values are medians and interquartile ranges or percentages. Pre-hospital time delay indicates time from onset of symptoms to arrival at coronary care unit; AMI, acute myocardial infarction; CK-MB, creatine kinase-MB isoenzyme; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate by MDRD; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

[a] *P* values were calculated on log-transformed data.

[b] During the first 7 days of hospital stay. To convert total cholesterol to conventional units (mg/dL) divide by 0.0259; eGFR (mL/min) by 0.0167.

analysis using increasing tertiles of LVEF showed a weaker interaction with gender than did Killip class (Table 2).

3.3. Survival and interaction analysis

The proportional-hazards assumption was verified for all variables used in the present surviving models ($P > 0.30$ for each variable). On univariable Cox regression analysis, female gender appeared to be associated with a higher CV risk than being male (Table 3). As expected, also Killip class (positively) and LVEF (negatively) were associated with higher mortality. After modeling the survival time controlling for age, mortality risk was no longer associated with female gender while it remained strongly associated with Killip class and LVEF (Table 3). Hence, a formal interaction term between gender and Killip class and LVEF was introduced into the survival models. This term revealed a negative interaction between female gender and Killip class for CV mortality (Table 3). The interaction was tested in five subsequent multivariable models after controlling for age, main CV risk factors, clinical features, post-discharge medical treatment, and mechanical coronary reperfusion. A significant negative interaction between female gender and increasing Killip class was found across all models (Table 3). The same steps were made using LVEF. At the univariable level, LVEF did not show a significant variation in hazard for female gender as compared to male gender. When the interaction was evaluated with controlling for age, the gender interaction became apparent. The adjustment for clinical and treatment variables of the subsequent models revealed a consistent significant positive interaction between female gender and increasing LVEF (Table 3). In Fig. 1, the graphical representation of interaction analysis shows the HR for CV mortality of men and women across Killip classes and LVEF. On univariable analysis, women with a lower degree of Killip class had higher risk than men while with increasing Killip class, they had lower risk than men (Fig. 1). After full adjustment of the model (using the same variables of the model in Table 3), the risk ratio maintained the same trend. LVEF at the univariable level did not show an interaction with gender, but after controlling for the abovementioned confounders, the interaction became clear (representation of full adjusted analysis is reported in Fig. 1).

Table 2
Interaction between gender and HF for the risk of 15-year CV mortality as assessed by Mantel–Haenszel test of homogeneity.

Mantel–Haenszel test of homogeneity by gender	Relative risks (95%CI) across Killip classes	*P* value
Men	2.4 (1.9–3.1)	
Women	1.3 (0.9–1.7)	
Overall	2.0 (1.6–2.4)	
Test of homogeneity		0.001
Mantel–Haenszel test of homogeneity by gender	**Relative risks (95%CI) across left ventricular ejection fraction tertiles**	***P* value**
Men	0.44 (0.33–0.59)	
Women	0.70 (0.51–0.97)	
Overall	0.53 (0.43–0.66)	
Test of homogeneity		0.03

4. Discussion

The main result of the ABC-3 Study on ACS is that women and men with ACS have different long-term CV mortality risk across increasing degrees of HF, even after controlling the survival models for age, main clinical features, and main treatments. Thus, gender is an independent effect modifier of HF for CV mortality.

Table 3
Survival analysis and variation in the effect of sex on the risk of 15-year CV mortality by Killip class and LVEF, and the effect of adding covariables.

Variable	Hazard ratio (95%CI)	*P* value
Female gender	1.8 (1.4–2.4)	<0.0001
Age-adjusted female gender	1.1 (0.8–1.5)	0.48
Killip class (3 classes)	2.6 (2.1–3.1)	<0.0001
Age-adjusted Killip class	1.9 (1.5–2.3)	<0.0001
LVEF (by tertiles)	0.57 (0.48–0.69)	<0.0001
Age-adjusted LVEF	0.62 (0.52–0.75)	<0.0001

Analysis of interaction between female gender and Killip class	Variation in hazard of death by gender (and 95%CI)	*P* value for gender – Killip class interaction
Unadjusted	0.51 (0.34–0.77)	0.002
Adjusted for age	0.62 (0.41–0.95)	0.03
Adjusted for the above and hypertension, diabetes, cholesterol	0.63 (0.42–0.96)	0.03
Adjusted for the above and heart rate, MDRD	0.64 (0.42–0.96)	0.03
Adjusted for the above and treatment with β-blocker, ACEI/AII inhibitor, statin, during follow-up	0.53 (0.33–0.85)	0.009
Adjusted for the above and thrombolysis on admission, PCI and CABG during follow-up	0.63 (0.42–0.95)	0.02

Analysis of interaction between female gender and LVEF		*P* value for gender – LVEF interaction
Unadjusted	1.4 (0.9–0.2.0)	0.11
Adjusted for age	1.5 (1.1–2.2)	0.04
Adjusted for the above and hypertension, diabetes, cholesterol	1.6 (1.1–2.3)	0.01
Adjusted for the above and heart rate, MDRD	1.7 (1.2–2.4)	0.006
Adjusted for the above and treatment with β-blocker, ACEI/AII inhibitor, statin, during follow-up	1.7 (1.2–2.5)	0.004
Adjusted for the above and thrombolysis (on admission), PCI and CABG during follow-up	1.7 (1.2–2.5)	0.005

LVEF indicates left ventricular ejection fraction; eGFR, estimated glomerular filtration rate by MDRD; CV, cardiovascular; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.

According to most of the studies in coronary disease, mortality rate after ACS is higher among women than men [5]. Age has emerged as an important confounding factor in the estimation of gender risk, but after controlling for age and other clinical variables, this difference tended to disappear [5,6]. Other studies, however, found that differences in short-term outcome between men and women could not be entirely accounted for by differences in baseline characteristics and could reflect pathophysiologic and anatomical differences between genders [9]. In patients with congestive HF, women have better survival than men, and that difference is stronger among patients with a non-ischemic etiology of HF [4]. In agreement, a recent meta-analysis showed that women with HF have a lower risk of death over a 3-year follow-up when compared with men with HF, in both preserved and reduced LVEF, chiefly in non-ischemic patients [11].

A key question is why women have different outcomes in relation to HF. There is a lack of studies comparing biological mechanisms of disease between men and women to better define vascular and pathophysiological processes that are unique to women [4,21–23]. Recent reports have highlighted important sex differences in the pathophysiology, presentation, and treatment of ischemic heart disease and have shown pervasive sex-related disparities in referral and treatment [9,10]. However, few studies have investigated sex-based differences in heart disease and ACS, and most of them dealt with short-term outcomes [21]. Age is an effect modifier in patients with myocardial infarction, and young and middle-aged women have worse outcome than men [8]. Even if younger women have a higher rate of risk factors, including history of HF, this higher rate does not entirely explain sex differences in outcome [22,24]. In the present study, the sequence of adjusted survival models, including progressively the main CV risk factors, clinical variables, and treatments, showed consistently that gender is an effect modifier in the association of HF degree during ACS and outcome. Even the type of myocardial infarction did not modify the interaction between gender and HF. Such an observation is in keeping with other reports showing that myocardial infarction type does not influence long term mortality [25]. Furthermore, it is of clinical relevance that the effect modification of sex is associated with a very long follow-up time, as the ABC-3 study lasted 15 years after the ACS event.

In the present study, women were less likely to receive thrombolytic therapy, PTCA, or CABG, compared with men. According to other reports, this observation can be due to their higher age and the higher rate of renal insufficiency [26]. However adjustment in surviving regressions by these treatments did not modify the interaction between gender and HF.

The two indicators of HF used in the present study, Killip class and LVEF, did not show a parallel association between gender and prognosis. Killip class degree appeared to modify the association of gender with CV risk, while LVEF measurement did not appear to interact with gender at univariable level. Only after controlling for age and a number of clinical variables the positive interaction with gender became clear. Accordingly, similar findings were found in patients hospitalized with HF, in whom long-term follow-up revealed a significant gender–LVEF interaction [27].

5. Limitations of the study

A major limitation of the ABC Study on Heart Disease is that at the time of patient enrollment, percutaneous coronary angioplasty was not currently in use for reopening coronary arteries in patients with STEMI. Thus, it remains uncertain whether early mechanical reperfusion might have modified the predictive models. However, we observed that the results of the predictive model were similar for patients with and without Q-wave myocardial infarction and those with and without thrombolytic treatment. Furthermore, adjustment of the survival models for medical and mechanical reperfusion treatment did not affect the results for gender interaction either with Killip class or LVEF.

Another limitation of the study is that diagnosis of myocardial infarction did not accounted troponin measurement, as it was not in use at that time, while we used as biochemical markers of necrosis the rise and gradual decline of creatine kinase and creatine kinase-MB. Nevertheless these markers of necrosis are still recommended in absence of troponin measurement [13].

Because this study was conducted in Caucasian patients, we cannot generalize these findings to other populations and ethnic groups.

6. Conclusion

Our findings support the hypothesis that gender modifies the impact of HF on prognosis long after ACS. Women with lower Killip class, or

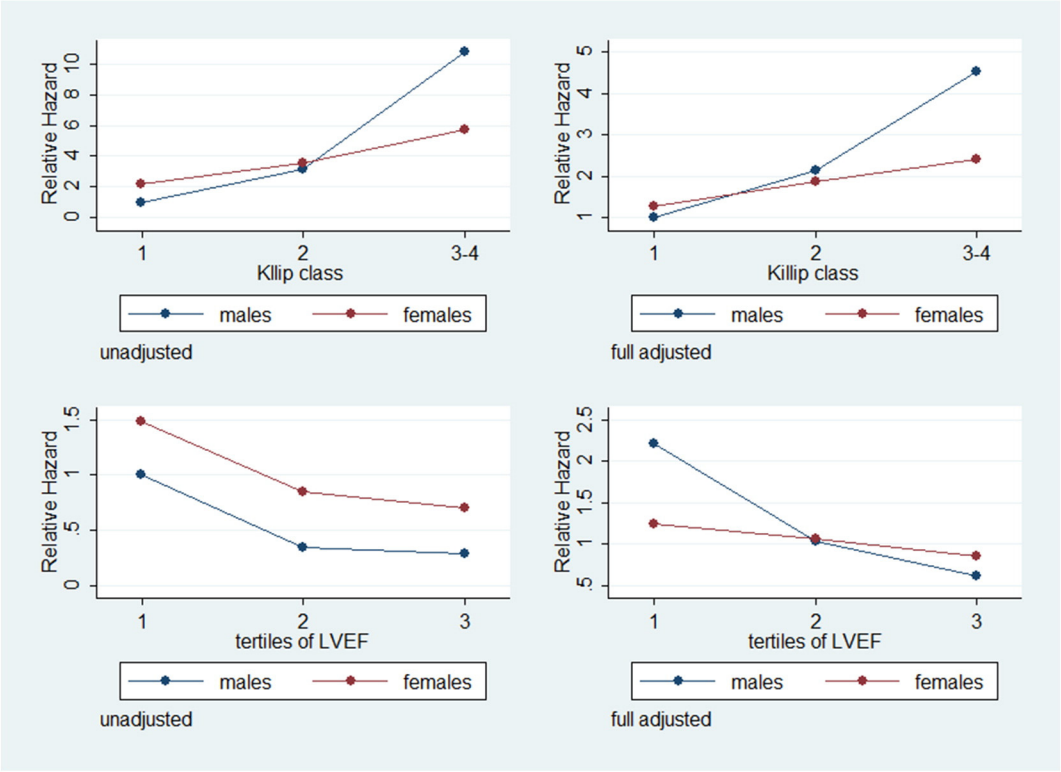

Fig. 1. Graphical representation of the interaction analysis showing the HRs for CV mortality of men and women across Killip classes and LVEF tertiles in patients followed 15 years after ACS. Left, unadjusted models; right, fully adjusted models.

higher LVEF, had higher CV mortality risk than men, and women with higher Killip class, or lower LVEF, had lower risk compared to men.

Author contributions

Dr. Berton designed the study. Dr. Cordiano and Dr. Palmieri contributed to the original data collection. Dr. Cavuto, Dr. Cordiano, and Dr. Cati contributed to data handling and patient follow-up. Dr. Cordiano and Dr. Pellegrinet contributed to the creation of the dataset and preparation of the tables and figure. Dr. Berton contributed to the analysis and interpretation of the data and the preparation of this manuscript. All authors contributed to the accuracy of the data analysis.

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Disclosures

None.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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