Archives of Cardiovascular Disease (2019) 112, 180—186

Available online at ScienceDirect www.sciencedirect.com

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CLINICAL RESEARCH

Evaluation of neutrophil gelatinase-associated lipocalin and cystatin C as biomarkers of acute kidney injury after ST-segment elevation myocardial infarction treated by percutaneous coronary intervention

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Received 5 June 2018; received in revised form 19 October 2018; accepted 4 November 2018
Available online 9 January 2019

KEYWORDS
STEMI;
Primary PCI;
Acute kidney injury;
Biomarkers;
Contrast volume

Summary
Background. — Two biomarkers of early acute kidney injury — plasmatic neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C — are not used in routine clinical practice in patients with ST-segment elevation myocardial infarction (STEMI) treated by percutaneous coronary intervention (PCI) because of a lack of supporting data.
Aims. — To evaluate the predictive value of NGAL and cystatin C regarding the incidence of contrast-induced acute kidney injury (CI-AKI) and clinical outcomes after STEMI in patients treated by primary PCI.

Abbreviations: AKIN, Acute Kidney Injury Network; AMI, acute myocardial infarction; CI-AKI, contrast-induced acute kidney injury; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; NGAL, neutrophil gelatinase-associated lipocalin; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

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https://doi.org/10.1016/j.acvd.2018.11.006

Methods. — Plasmatic NGAL and cystatin C were measured on admission, before any contrast exposure, in 701 unselected patients with STEMI. Associations between biomarker concentrations and incidence of CI-AKI (assessed at 48 h), haemodialysis requirement at 1 year and all-cause mortality at 1 year were assessed by logistic regression analyses and receiver operating characteristic area under the curve analysis (*c*-statistic). Discrimination performance comparison was performed using the DeLong test.
Results. — NGAL and cystatin C had mild discrimination regarding CI-AKI, with c-statistics of 0.60 ($P = 0.001$) and 0.60 ($P = 0.002$), respectively. Combining NGAL and cystatin C did not improve their discrimination (*c*-statistic 0.61; $P = 0.001$). There was no significant difference in discrimination between NGAL, cystatin C and baseline creatinine ($P = 0.57$). Regression analyses showed no independent association between NGAL and CI-AKI, haemodialysis or 1-year mortality. Similarly, cystatin C was not associated with these clinical outcomes.
Conclusions. — In this cohort of patients with STEMI treated by primary PCI, plasmatic NGAL and cystatin C did not provide additional value regarding CI-AKI prediction compared with known risk factors such as baseline creatinine.

Background

Contrast-induced acute kidney injury (CI-AKI) is a prevalent complication of acute myocardial infarction (AMI) treated by urgent primary percutaneous coronary intervention (PCI), which exposes the patient to contrast media. CI-AKI occurs in 10—20% of patients [1,2]. This silent complication, characterized by a transient increase in serum creatinine (or a decrease in estimated glomerular filtration rate [eGFR]), is associated with increased morbidity and mortality [3—8]. Research into kidney biomarkers to track kidney injury or estimate prognosis is ongoing, and potential candidates have been identified.

Cystatin C, a small non-glycosylated 13 kDa basic protein, was suggested as an alternative filtration marker to creatinine, and was reported as an early marker of CI-AKI (i.e. of glomerular filtration before any elevation of serum creatinine) [9]. Neutrophil gelatinase-associated lipocalin (NGAL), a 25-kDa protein covalently bound to gelatinase from human neutrophils, was reported as a marker of kidney tubular injury, and was nicknamed ''kidney troponin'' for similar reasons [10]. Currently, these biomarkers are not used in routine clinical practice because of a lack of supportive data over classical risk factors or controversies [11].

The present study aimed to evaluate the ability of cystatin C and NGAL to predict the incidence of CI-AKI in patients with AMI, when measured on arrival before contrast media exposure. AMI is a high-risk situation exposing patients to CI-AKI as a result of haemodynamic changes, the absence of pre-emptive hydration and the use of a potentially high volume of contrast media [12,13]. Both biomarkers correlated with clinical outcome in patients with coronary disease in small-sample studies [10,14,15], but data in AMI remain scarce. The objectives of the present study were to evaluate the diagnostic performances of the plasma concentrations of NGAL and cystatin C measured on admission to identify CI-AKI, and to evaluate their prognostic performance in a large cohort of patients with AMI treated with primary PCI.

Methods

Patient population

This study was designed as a prospective observational cohort, and included consecutive patients with STEMI admitted for primary PCI at the Pitié-Salpêtrière University Hospital, Paris, France. Patients without a final diagnosis of STEMI at angiography or with chronic haemodialysis or peritoneal dialysis were excluded.

STEMI protocol

Primary PCI was performed using the radial approach as the default strategy. All patients received aspirin and anticoagulation before transfer to the catheterization laboratory, and were loaded with a P2Y12 inhibitor as soon as possible. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of physicians. To avoid overuse of contrast media, systematic echocardiography on admission was encouraged, whereas ventriculography was not recommended. Postprocedural hydration was recommended with 1000 mL of physiological (0.9%) saline given intravenously (rate of 0.6 mL/kg per hour for 24 hours) to all patients except those in Killip class III or IV. N-acetylcysteine and sodium bicarbonate solution (NaHCO3) were not used. All procedures were performed with a low-osmolar ionic dimer (Hexabrix™; Guerbet, Villepinte, France). Maximum contrast dose (in mL) was computed as the ratio of body weight (kg) × 5/serum creatinine (mg/dL), and the contrast ratio as amount of contrast administered/maximum contrast dose [16].

Measurement of biomarkers and evaluation of AKI

Blood samples were obtained via radial sheath before contrast injection, and platelet-poor plasma was aliquoted and frozen for further analysis. Cystatin C concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) with a commercially available kit (Quantikine® ELISA, human cystatin C; R&D Systems, Minneapolis, MN, USA). The mean minimum detectable dose was 0.102 ng/mL. Intra-assay precision was < 7% and interassay precision was < 7%. NGAL concentrations were determined using an ELISA with a commercially available kit (Quantikine® ELISA, human lipocalin-2/NGAL; R&D Systems, Minneapolis, MN, USA). The mean minimum detectable dose was 0.012 ng/mL. Intra-assay precision was < 5% and interassay precision was < 8%. The serum creatinine concentration was measured on admission, before administration of any contrast agent, and on every day after that until discharge.

Demographic and clinical data were entered into the e-PARIS registry using electronic medical records. Special attention was given to haemodynamic instability, defined by the presence of one of the following events at initial care: cardiogenic shock, use of inotropic drugs, use of intra-aortic balloon pump or the presence of complete atrioventricular block. Comorbidities and risk profiles were defined for each patient according to the Thrombolysis In Myocardial Infarction (TIMI) risk score for STEMI. Systematic follow-up, using visits and phone calls, continued for 12 months after hospital discharge, recording the occurrence of cardiovascular events, the need for haemodialysis and all-cause mortality.

Definitions and study objectives

Patients were assessed for the presence of CI-AKI 48 hours after admission using the Acute Kidney Injury Network (AKIN) definition (a +0.3 mg/dL [26.5 μmol/L] or + 50% relative increase in serum creatinine) [17]. Similarly, the severity of AKI was staged using the AKIN classification (stage one defined as described above, stage two as a + 100% increase in serum creatinine and stage three as a + 200% increase in serum creatinine). eGFR was calculated using the Modification of Diet in Renal Disease study formula. Serum creatinine sampled on admission was considered as baseline, and was compared with serum creatinine sampled 48 hours after admission.

Other clinical endpoints included all-cause mortality and the need for haemodialysis at 1-year follow-up.

Statistical analysis

Continuous variables are presented as means ± standard deviations. All variables were analysed for normality distribution. Intergroup comparisons were performed using the t test or the Mann—Whitney U test, as appropriate. Categorical variables are expressed as rates or proportions, and were compared using the χ^2 test or Fisher's exact test, as appropriate.

The discriminative accuracy of NGAL and cystatin C was assessed by computing the receiver operating characteristic area under the curve (*c*-statistic). The associations of NGAL and cystatin with CI-AKI incidence, haemodialysis and mortality were evaluated using logistic regression analyses. Confounding variables added to the multivariable models included: age; baseline renal impairment (eGFR < 60 mL/min); haemodynamic instability; diuretic use during hospitalization; known coronary artery disease; treatment with angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors; troponin; NGAL; and cystatin C.

Given that previous studies found different discrimination performances for NGAL and cystatin C, and with an incidence of CI-AKI ranging from 10% to 20% depending on definitions [18], it was assumed that to assert a correct c-statistic, a minimum number of 594 patients would be required, i.e. with a CI-AKI incidence of 10% and a c-statistic of 0.6 for the tested biomarkers (considered clinically relevant), for a type I error of 0.05 and power of 0.8. IBM SPSS Statistics statistical software, version 23.0 (SPSS Inc., Chicago, IL, USA) was used for all calculations.

Results

Study population

Demographic and procedural data are presented in Table 1. Overall, 701 patients were included. The study population is representative of unselected patients with STEMI, with 13.4% presenting with haemodynamic instability, 4.9% with out-of-hospital cardiac arrest and 12.0% with a TIMI risk score > 6. There were no missing data.

Incidence of CI-AKI

A total of 84 (12.0%) patients developed CI-AKI during hospitalization. A comparison between patients who developed CI-AKI and those who did not is presented in Table 1.

There was no difference in volume of contrast media in the CI-AKI group versus the no CI-AKI group (211 ± 65 mL vs. 209 ± 68 mL, respectively; $P = 0.69$) and < 10% of patients received ≥ 300 mL of contrast media. The maximum tolerated contrast media volume was lower in patients who developed CI-AKI than in those who did not (398 ± 175 mL vs. 436 ± 142 mL; $P = 0.004$), resulting in a higher proportion of patients with a contrast ratio > 1 (14.3% vs. 5.2%; $P = 0.002$). Indeed, a contrast ratio > 1 was a potent risk factor for developing CI-AKI, with an unadjusted odds ratio of 3.3 (95% confidence interval 1.6—6.6; $P = 0.001$), although it was not independently associated after adjusting for confounding variables.

Patients who developed CK-AKI were more frequently treated with haemodialysis (14.9% vs. 2.4%; $P < 0.0001$) at 1-year follow-up, and had a higher mortality rate (33.3% vs. 8.6%; $P < 0.0001$) than patients who did not develop CI-AKI.

Discrimination performance of biomarkers regarding CI-AKI

The discrimination performance of baseline creatinine regarding the incidence of CI-AKI was mild, with a c-statistic of 0.57 ($P = 0.02$). The discrimination performances of NGAL and cystatin C had c-statistics of 0.60 ($P = 0.001$) and 0.60

Table 1 Baseline characteristics and comparison between patients who presented contrast-induced acute kidney injury and those who did not.

	No CI-AKI ($n = 617$)	CI-AKI ($n = 84$)	P[a]
Male sex	464 (75.2)	59 (70.2)	0.35
Age (years)	62.8 ± 14.4	68.9 ± 12.8	< 0.01
Elderly patient, aged > 75 years	147 (23.8)	33 (39.3)	< 0.01
Body mass index	13.9 ± 0.3	26.0 ± 4.1	0.6
LVEF (%)	53.3 ± 11.0	44.4 ± 12.0	< 0.0001
Clinical presentation			
SBP (mmHg)	128.9 ± 25.2	127.1 ± 30.1	0.53
Heart rate (beats/min)	79.6 ± 16.4	82.9 ± 21.1	0.05
Haemodynamic instability	61 (9.9)	33 (39.3)	< 0.0001
Cardiac arrest	23 (3.7)	11 (13.1)	< 0.01
Killip stage > II	36 (5.8)	17 (20.2)	< 0.0001
TIMI risk score > 6	59 (9.6)	25 (29.8)	< 0.0001
Comorbidities			
High blood pressure	263 (42.6)	47 (56)	0.04
Dyslipidaemia	235 (38.1)	38 (45.2)	0.23
Active smoking	251 (40.7)	24 (28.5)	0.04
Diabetes	114 (18.4)	20 (23.8)	0.24
Known coronary artery disease	102 (16.5)	27 (32.1)	< 0.01
Renal insufficiency (eGFR < 60)	137 (22.2)	31 (36.9)	0.01
Severe renal insufficiency (eGFR < 30)	22.8 (3.7)	7 (8.3)	0.08
Medication during hospitalization			
ACEI/ARB	495 (80.2)	56 (66.7)	0.01
Beta-blocker	491 (79.6)	51 (60.7)	< 0.001
Diuretic	98 (15.2)	39 (46.4)	< 0.0001
PCI			
Multivessel disease	110 (17.9)	25 (30.3)	0.02
Contrast (mL)	210.6 ± 65.2	208.9 ± 67.6	0.69
Contrast > 300 mL	55 (8.9)	10 (11.7)	0.4
Contrast ratio > 1	32 (5.2)	12 (14.3)	< 0.01
Biomarkers			
Troponin peak (μg/mL)	73.1 ± 144.3	192.5 ± 493.1	0.03
Baseline creatinine	82.7 ± 36.2	106.1 ± 85.7	< 0.001
Baseline eGFR (mL/min)	90.8 ± 25.3	78.6 ± 27.6	< 0.0001
Cystatin C (ng/mL)	1041 ± 895.7	1303 ± 1053	< 0.001
NGAL (ng/mL)	243.7 ± 192.1	338.7 ± 259.6	< 0.001

Data are expressed as number (%) or mean ± standard deviation. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor inhibitor; CI-AKI: contrast-induced acute kidney injury; eGFR: estimated glomerular filtration rate, calculated with the Modification of Diet in Renal Disease study formula; LVEF: left ventricular ejection fraction; NGAL: neutrophil gelatinase-associated lipocalin; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; TIMI: Thrombolysis In Myocardial Infarction.
[a] Intergroup comparison P values.

($P = 0.002$), respectively (Fig. 1). The combination of NGAL and cystatin C did not improve their discriminative performance, with a c-statistic of 0.61 ($P = 0.001$). There was no difference between the discrimination performances of baseline creatinine, NGAL and cystatin C (DeLong comparison, $P = 0.57$).

Although associated with CI-AKI in the univariate analysis, after adjusting for confounding variables (age, haemodynamic instability, impaired baseline eGFR, multivessel disease, troponin and treatment with angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors or diuretics), neither NGAL nor cystatin C was associated with CI-AKI (Table 2) in the multivariable analysis.

Prognostic performance of biomarkers

Although in the univariate regression analysis, NGAL was associated with haemodialysis requirement at 1 year (unadjusted odds ratio [per 1 ng/mL increase] 1.002, 95% confidence interval 1.000—1.003; $P = 0.023$), this was not the case after adjusting for baseline creatinine. Cystatin C was not associated with 1-year haemodialysis requirement in the univariate regression analysis.

Similarly, although the univariate survival analysis showed that patients with higher tertiles of NGAL and cystatin had higher rates of 1-year mortality, after adjustment for confounding variables, in the multivariable analysis,

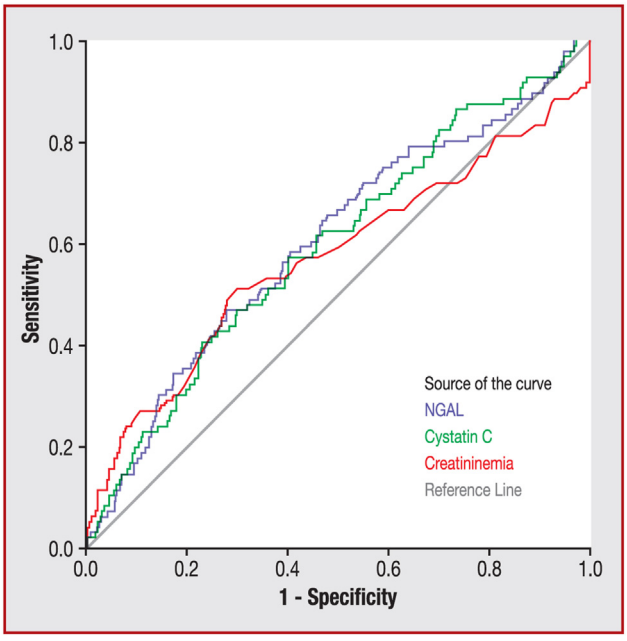

Figure 1. Comparison of the discrimination performance of neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C regarding the incidence of contrast-induced acute kidney injury. NGAL is in blue, cystatin C in green and baseline creatinine in red. The respective c-statistics are 0.60 ($P = 0.001$), 0.60 ($P = 0.002$) and 0.57 ($P = 0.02$).

neither NGAL nor cystatin C was associated with 1-year mortality (Table 3).

Discussion

CI-AKI is a frequent complication in AMI, associated with higher morbidity, longer hospitalization stays and higher mortality. Early detection of CK-AKI may allow better care, and may potentially avoid its detrimental consequences on clinical outcome. Unfortunately, there are only limited data on CI-AKI biomarkers in the setting of patients with STEMI treated by primary PCI. In the current study, we evaluated the diagnostic and prognostic performances of the biomarkers NGAL and cystatin C, measured on admission, in identifying CI-AKI in patients with AMI.

The results of the present work can be summarized as follows:

- NGAL and cystatin C had similar discrimination performances compared with baseline creatinine;
- after adjusting for confounding factors in the multivariable regression analysis, neither NGAL nor cystatin C was associated with CI-AKI;
- neither NGAL nor cystatin C was associated with 1-year all-cause mortality or 1-year haemodialysis requirement.

A recent meta-analysis of 14 studies with 1520 patients demonstrated that NGAL after PCI was accurate in predicting the occurrence of CI-AKI, with a pooled c-statistic of 0.93 [19]. In this cohort of patients with STEMI treated by primary PCI, NGAL had a c-statistic of 0.60, a value seemingly too low to allow routine clinical use. Although patients with the highest values of NGAL ($\geq$ 255 ng/mL) displayed a twofold increase in CI-AKI, this association was not independent from baseline creatinine.

In terms of the prognostic value of plasmatic NGAL and cystatin C regarding patient outcomes, those with the highest values of NGAL (> 255 ng/mL) and cystatin C (> 1048 ng/mL) had a higher rate of 1-year mortality. Again, after adjusting for known prognostic factors for myocardial infarction severity, such as renal impairment, none of the biomarkers was independently associated with mortality, making them less relevant.

Table 2 Variables associated with the incidence of contrast-induced acute kidney injury before and after adjustment, in logistic regression analyses.

	Unadjusted OR	95% CI	Unadjusted *P*	Adjusted OR	95% CI	Adjusted *P*
Haemodynamic instability	5.3	3.24—8.71	< 0.001	3.1	1.79—5.29	< 0.001
Diuretic use during hospitalization	5.8	3.65—9.18	< 0.001	4.0	2.38—6.57	< 0.001
Known coronary artery disease	2.3	1.43—3.76	0.001	2.3	1.34—4.01	0.002
Upper troponin tertile (> 75 μg/mL)	2.4	1.53—3.66	< 0.001	2.4	1.48—3.97	< 0.001
ACEI/ARB use	0.61	0.38—0.99	0.047	0.56	0.33—0.97	0.04
Age (per year)	1.0	1.03—1.06	< 0.001	1.03	1.01—1.05	0.002
Baseline renal impairment (eGFR < 60)	2.5	1.61—3.97	< 0.001	-	-	NS
Upper NGAL tertile (> 255 ng/mL)	2.0	1.28—3.05	0.002	-	-	NS
Upper cystatin-C tertile (> 1048 ng/mL)	1.9	1.25—2.98	0.003	-	-	NS
Contrast ratio > 1	3.3	1.63—6.57	0.001	-	-	NS

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CI: confidence interval; eGFR: estimated glomerular filtration rate (mL/min/kg); NGAL: neutrophil gelatinase-associated lipocalin; NS: not significant; OR: odds ratio.

Table 3 Variables associated with the incidence of 1-year mortality before and after adjustment, in logistic regression analyses.

	Unadjusted OR	95% CI	Unadjusted *P*	Adjusted OR	95% CI	Adjusted *P*
Cardiac arrest	8.3	4.0—16.9	< 0.0001	6.2	2.43—16.0	< 0.0001
Haemodynamic instability	7.7	4.6—13.0	< 0.0001	4.1	2.22—7.76	< 0.0001
LVEF < 40%	4.7	2.7—8.0	< 0.0001	2.6	1.36—5.05	0.004
Baseline renal impairment (eGFR < 60)	4	2.5—6.4	< 0.0001	2.8	1.38—5.58	0.004
Age > 75 years	3	1.9—4.8	< 0.0001	2.2	1.09—4.43	0.03
Upper NGAL tertile (> 255 ng/mL)	2.4	1.53—3.89	< 0.0001	-	-	NS
Upper cystatin-C tertile (> 1048 ng/mL)	2.5	1.58—4.03	< 0.0001	-	-	NS
ACEI/ARB use	0.36	0.22—0.59	< 0.0001	0.46	0.25—0.86	0.014

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CI: confidence interval; eGFR: estimated glomerular filtration rate (mL/min/kg); LVEF: left ventricular ejection fraction; NGAL: neutrophil gelatinase-associated lipocalin; NS: not significant; OR: odds ratio.

The results of this study confirm those of recent trials performed in patients with heart failure, where both biomarkers were evaluated as predictors of worsening of renal function and clinical adverse events. In these studies, NGAL and cystatin C assessed at baseline were associated with clinical endpoints, but neither added significant diagnostic utility over the classical clinical evaluation after adjustment for baseline characteristics, such as first creatinine measurement [20,21].

As several factors may contribute to the incidence of AKI after a myocardial infarction, the definition of CI-AKI itself has to be cautious. Indeed, the criterion chosen in this study for CI-AKI was the AKIN definition, because of its widespread use, but the incidence of CI-AKI can vary widely depending on the chosen definition. In a previous publication, we confirmed the accuracy and relevance of the AKIN definition regarding CI-AKI, thus justifying its use in the present paper [18].

Regardless of the definition, the performance of NGAL and cystatin C in the present cohort was not considered clinically relevant compared with baseline creatininaemia and other known risk factors for AKI. This finding adds to the already long corpus of publications advocating against the use of such biomarkers in the critical care setting, emphasizing the poor discrimination performance in the specific context of myocardial infarction and the use of contrast media agents.

Study limitations

We acknowledge several limitations. First, the single-centre nature of this cohort requires external validation; however, previous publications on CI-AKI suggest that standard care for these patients is similar between the present cohort and others [18]. Second, although haemodynamic instability may represent an extreme situation for these biomarkers, when organ failure is a key player for survival, we believe that biomarkers need to be proven in an all-comer population, without exclusion criteria, and especially in those with haemodynamic impairment. Third, papers have suggested the use of serial measurements for NGAL and cystatin C, with the potential added value of a kinetic rather than a one-point measurement. However, in acute care settings, such as in cardiac intensive care units, repeated assessments were not proven to be more effective [22].

Conclusion

In this cohort of patients with STEMI treated by primary PCI, neither plasmatic NGAL nor cystatin C were independent risk factors for CI-AKI; in addition, they were not independently associated with 1-year mortality or haemodialysis requirement at 1 year.

Disclosure of interest

L. S. N. Research grants from the Fédération Française de Cardiologie.

M. K. Research grants from the Fédération Française de Cardiologie, the Société Française de Cardiologie and the company Sanofi. Lecture and consulting fees from the European Society of Cardiology and the companies AstraZeneca, Bayer and Daiichi-Sankyo.

J.-P. C. Research grants or honoraria from the Fédération Française de Cardiologie and the companies AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, Lead-Up, Medtronic, MSD, Sanofi-Aventis and WebMD.

G. M. Research grants or honoraria from Brigham Women's Hospital, the Cardiovascular Research Foundation, CME Resources, the Fédération Française de Cardiologie, the Fondazione Anna Maria Sechi per il Cuore, the TIMI Study Group and the companies ADIR, Amgen, AstraZeneca, Bayer, Berlin Chimie AG, Boehringer Ingelheim, Bristol-Myers Squibb, Beth Israel Deaconess Medical, Celladon, Daiichi-Sankyo, Eli Lilly, Europa, Elsevier, Gilead, ICAN, Janssen, Lead-Up, Menarini, Medtronic, MSD, Pfizer, Sanofi-Aventis, Servier, The Medicines Company and WebMD.

J. S. Research grants, honoraria or travel support from the Fondation de France and the companies Actelion, Amed,

Amgen, Algorythm, AstraZeneca, Bayer, Daiichi-Sankyo, Eli Lilly, Gilead Science, Iroko Cardio, Sanofi-Aventis and St. Jude Medical.

The other authors declare that they have no conflicts of interest concerning this article.

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