ESC European Society of Cardiology

European Heart Journal (2018) **0**, 1–14
doi:10.1093/eurheartj/ehy127

CLINICAL RESEARCH
Acute Coronary Syndromes

Predicting the development of in-hospital cardiogenic shock in patients with ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention: the ORBI risk score

Vincent Auffret[1]*, Yves Cottin[2], Guillaume Leurent[1], Martine Gilard[3], Jean-Claude Beer[2], Amer Zabalawi[4], Frédéric Chagué[2], Emanuelle Filippi[5], Damien Brunet[6], Jean-Philippe Hacot[7], Philippe Brunel[6], Mourad Mejri[8], Luc Lorgis[2], Gilles Rouault[9], Philippes Druelles[10], Jean-Christophe Cornily[11], Romain Didier[3], Emilie Bot[12], Bertrand Boulanger[13], Isabelle Coudert[14], Aurélie Loirat[1], Marc Bedossa[1], Dominique Boulmier[1], Maud Maza[2], Marielle Le Guellec[1], Rishi Puri[1], Marianne Zeller[15], and Hervé Le Breton[1]; On behalf of the ORBI and RICO Working Groups

[1]Department of Cardiology and Vascular Diseases, Pontchaillou University Hospital, Center for Clinical Investigation 804, University of Rennes 1, Signal and Image Treatment laboratory (LTSI), National Institute of Health and Medical Research U1099, Rennes, France; [2]Department of Cardiology, University Hospital of Dijon-Burgundy, 5 boulevard Jeanne d'Arc, 21000 Dijon, France; [3]Department of Cardiology, La Cavale Blanche University Hospital, Optimization of physiological Regulations, Science and Technical Training and ResearchUnit, Boulevard Tanguy Prigent, 29200 Brest, France; [4]Department of Cardiology, General Hospital Yves Le Foll, 10 Rue Marcel Proust, 22000 St-Brieuc, France; [5]Department of Cardiology, General Hospital of Atlantic Brittany, 20 Boulevard du Général Maurice Guillaudot, 56017 Vannes, France; [6]Department of Cardiology, Clinic of Fontaine, 1 Rue des Creots, 21121 Fontaine-lès-Dijon, France; [7]Department of Cardiology, General Hospital of South Brittany, 5 Avenue Choiseul, 56322 Lorient, France; [8]Department of Cardiology, General Hospital Broussais, St-Malo, 1 Rue de la Marne, 35403 France; [9]Department of Cardiology, General Hospital René Théophile Laennec, 14 bis Avenue Yves Thépot, 29107 Quimper, France; [10]Department of Cardiology, Clinic St-Laurent, 320 Avenue Général George S. Patton, 35700 Rennes, France; [11]Department of Cardiology, Clinic Keraudren-Grand Large, 375 Rue Ernestine de Trémaudan, 29220 Brest, France; [12]Department of Medical Emergency, Pontchaillou University Hospital, 2 Rue Henri Le Guilloux, 35033 Rennes, France; [13]Department of Medical Emergency, General Hospital of Atlantic Brittany, 20 Boulevard du Général Maurice Guillaudot, 56017 Vannes, France; [14]Department of Medical Emergency, General Hospital Yves Le Foll, 10 Rue Marcel Proust, 22000 St-Brieuc, France; and [15]EA 7460 Cerebro- and Cardiovascular Physiopathology and Epidemiology, University of Bourgogne-Franche Comté, 7 Boulevard Jeanne d'Arc, 21000 Dijon, France

Received 28 October 2017; revised 14 December 2017; editorial decision 23 February 2018; accepted 23 February 2018

Aims To derive and validate a readily useable risk score to identify patients at high-risk of in-hospital ST-segment elevation myocardial infarction (STEMI)-related cardiogenic shock (CS).

Methods and results In all, 6838 patients without CS on admission and treated by primary percutaneous coronary intervention (pPCI), included in the Observatoire Régional Breton sur l'Infarctus (ORBI), served as a derivation cohort, and 2208 patients included in the obseRvatoire des Infarctus de Côte-d'Or (RICO) constituted the external validation cohort. Stepwise multivariable logistic regression was used to build the score. Eleven variables were independently associated with the development of in-hospital CS: age >70 years, prior stroke/transient ischaemic attack, cardiac arrest upon admission, anterior STEMI, first medical contact-to-pPCI delay >90 min, Killip class, heart rate >90/min, a combination of systolic blood pressure <125 mmHg and pulse pressure <45 mmHg, glycaemia >10 mmol/L, culprit lesion of the left main coronary artery, and post-pPCI thrombolysis in myocardial infarction flow grade <3. The score derived from these variables allowed the classification of patients into four risk categories: low (0–7), low-to-intermediate (8–10), intermediate-to-high (11–12), and high (≥13). Observed in-hospital CS rates were 1.3%, 6.6%, 11.7%, and 31.8%, across the four risk categories, respectively. Validation in the RICO cohort demonstrated in-hospital CS rates of 3.1% (score 0–7), 10.6% (score 8–10), 18.1% (score 11–12), and 34.1% (score ≥13). The

* Corresponding author. Tel: + 33 299 282 505, Fax: +33 299 282 529, Email: vincent.auffret@chu-rennes.fr

score demonstrated high discrimination (c-statistic of 0.84 in the derivation cohort, 0.80 in the validation cohort) and adequate calibration in both cohorts.

Conclusion The ORBI risk score provides a readily useable and efficient tool to identify patients at high-risk of developing CS during hospitalization following STEMI, which may aid in further risk-stratification and thus potentially facilitate pre-emptive clinical decision making.

Keywords ST-segment elevation myocardial infarction • Cardiogenic shock • Risk score • Predictors

Introduction

Despite improvements in the acute management of ST-segment elevation myocardial infarction (STEMI), particularly the widespread use of timely primary percutaneous coronary intervention (pPCI), cardiogenic shock (CS) in this setting still portends a dismal prognosis with 30-day mortality rates approximating 40–45%.[1–4] While its incidence declined in parallel with the advent of pPCI, CS continues to complicate 2.5% of acute coronary syndromes[3,5] and 5–15% of STEMI,[1,2,4,6] thus translating into 40–50 000 annual cases in the USA and 60–70 000 patients/year in Europe.[1,7]

Clinical trials testing the use of additional therapies on top of early revascularization of the culprit lesion [immediate multivessel PCI, intra-aortic balloon pump (IABP) or Impella], in the setting of ischaemic CS, failed to demonstrate meaningful reductions in short- to mid-term mortality.[8–11] These results suggest that once the deleterious physiopathological spiral of CS has begun,[12] little prognostic improvement is expected despite invasive medical interventions. Furthermore, mechanical and pharmacological strategies aimed at improving STEMI outcomes, recently evaluated in randomized trials, also failed to reduce infarct size, the incidence of CS, and ultimately short- or mid-term mortality in all-comers populations of anterior STEMI patients.[13,14] Overall, these data suggest that adjunctive therapies may only be beneficial in patients at high-risk for CS, for whom no reliable risk score currently exists.

From large multicentre registries, we aimed to develop a risk score predicting the in-hospital occurrence of CS amongst STEMI patients treated with pPCI without CS on admission, which in turn could help to better identify patients with impending CS who likely stand to benefit the most from the early initiation of adjunctive therapeutic strategies.

Methods

Data collection

Data from the previously described Observatoire Régional Breton sur l'Infarctus (ORBI)[15] were used as a derivation cohort. Briefly, ORBI prospectively includes all patients admitted to any of the nine interventional cardiology centres (*Supplementary material online*) in Brittany, France for STEMI (final diagnosis) within 24 h of symptoms' onset. The database used for this study contains demographic and electrocardiographic data, treatments, time intervals, and in-hospital events. For external validation purposes, the database from another administrative French region, obseRvatoire des Infarctus de Côte-d'Or (RICO),[16] was used. The RICO survey prospectively collects in-hospital data from patients hospitalized with acute myocardial infarction in the two cardiac intensive care units of Côte-d'Or region (*Supplementary material online*). These surveys were approved by French National Commission of Informatics and Civil Liberties and the study protocol was approved by local ethics committees.

Patients

Patients enrolled in ORBI between June 2006 and December 2015 without CS on admission and treated with pPCI, were included in this analysis (*Figure 1*) to develop the risk-scoring system. Using the same inclusion criteria, patients enrolled in RICO between January 2002 and June 2016, with complete data regarding risk factors identified in the derivation cohort, were included in the validation cohort.

Definitions

ST-segment elevation myocardial infarction was defined according to the universal definition of myocardial infarction.[17] Because classic haemodynamic measurements of CS (systolic blood pressure ≤90 mmHg with cardiac index <1.8 L/min/m^2 without support or <2.0 to 2.2 L/min/m^2 with support and left ventricular end-diastolic pressure >18 mmHg or right ventricular end-diastolic pressure >10 to 15 mmHg)[18] are rarely available in routine practice, CS was defined as systolic blood pressure ≤90 mmHg for >30 min following exclusion of hypovolaemia, with clinical evidence of hypoperfusion, inotrope dependence, or mechanical left ventricular support to correct this situation, as diagnosed by the treating physician. Cardiogenic shock was considered present on admission if diagnosed during pre-hospital management by mobile intensive care units or on the first medical exam performed upon admission before pPCI in patients directly admitted in emergency departments. Patients presenting with CS on admission were excluded from the analysis.

Statistical analysis

Data are summarized as number (percentages) for categorical variables. Continuous variables are expressed as median (interquartile range). Qualitative data were compared using the χ^2 or Fisher exact tests while quantitative data were compared using the Mann–Whitney *U* test. All tests were 2-sided at the 0.05 significance level.

The derivation cohort was used to identify predictors of in-hospital occurrence of CS and to develop a risk-scoring system which was tested in the validation cohort. Univariable logistic regression with the development of in-hospital CS as the dependent variable was performed on complete cases. Receiver–operator curves were used to categorize continuous variables with a *P*-value <0.05 in univariable analysis by selecting clinically relevant cut-offs, which were the closest to the optimal cut-off according to the Youden's index. Overall, 1.03% of data were missing and a total of 26.3% of patients had at least 1 missing value. For the purposes of multivariable analysis, assuming missing data were randomly missing, multiple imputation using Monte Carlo Markov chained

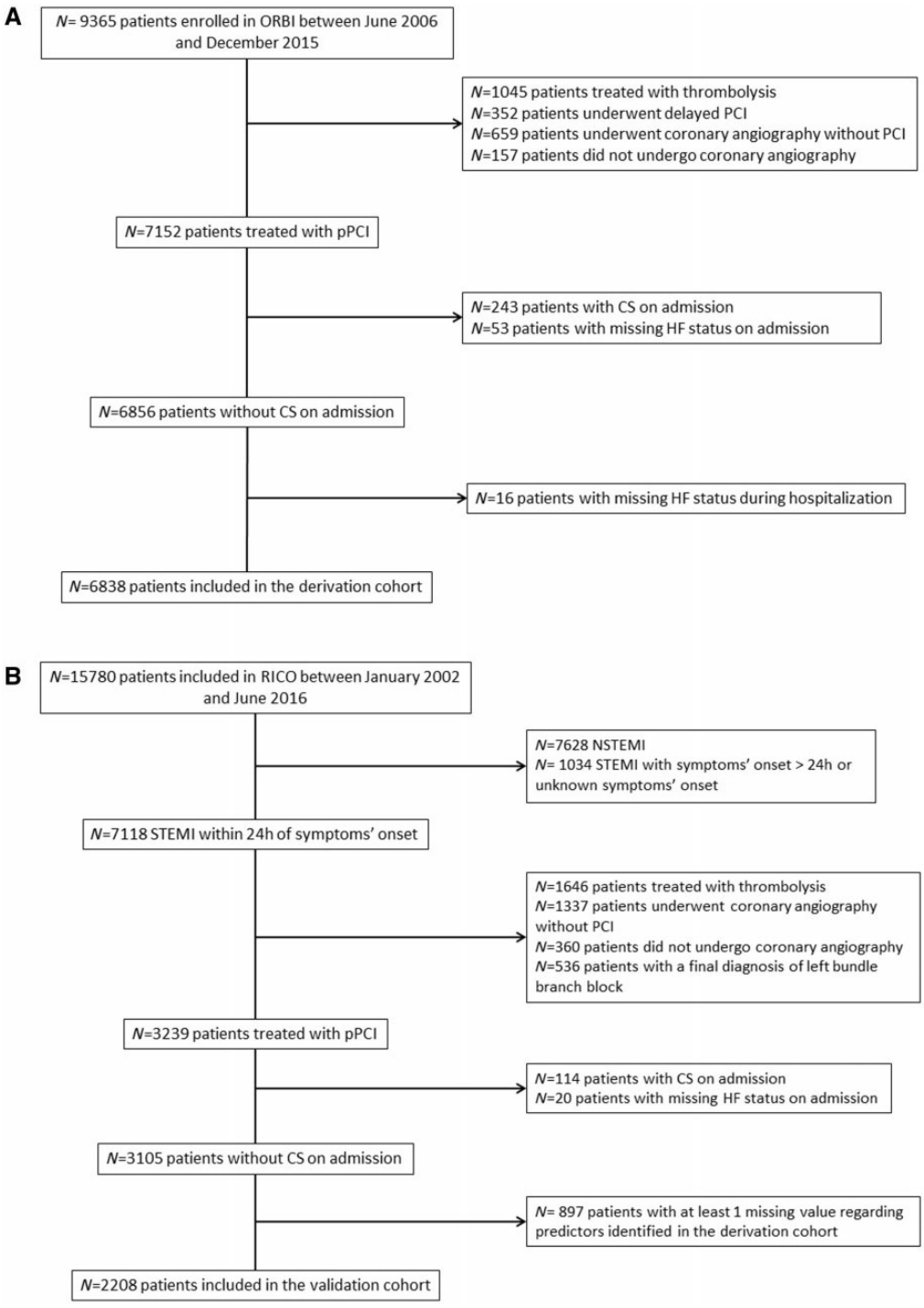


Figure 1 Flowcharts of the derivation and validation cohort. The derivation cohort (*A*) comprised patients included in the ORBI whereas the validation cohort (*B*) was from the RICO. CS, cardiogenic shock; HF, heart failure; NSTEMI, non-ST-segment elevation myocardial infarction; ORBI, Brittany Regional Infarction Observatory; pPCI, primary percutaneous coronary intervention; RICO, Côte-d'Or Regional Infarction Observatory; STEMI, ST-segment elevation myocardial infarction.

equations[19] was used to generate 20 data sets without missing values. Variables with a *P*-value <0.05 in univariable analysis were entered in a multivariable logistic regression model to derive adjusted odds ratio (OR) with 95% confidence intervals (95% CI) which were then combined using Rubin's rule.[19] A stepwise process was applied to identify the best parsimonious set of predictors. To allow the creation of a readily useable risk score in routine practice, creatinine level on admission, which may not be available at the end of a pPCI procedure, was not included in the model. Moreover, procedural variables depending on the operator's choice and likely influenced by patient's presentation such as access site

Table 1 Baseline, procedural characteristics, and in-hospital outcomes in the derivation and validation cohorts

Variables	Derivation cohort (*n* = 6838)	Validation cohort (*n* = 2208)	*P*-value
Baseline characteristics			
Clinical characteristics			
Age (years)	62 (53–73)	64 (54–77)	<0.001
Female sex	1519 (22.2)	634 (28.7)	<0.001
Body mass index (kg/m^2)	26 (24-29), n = 6680	26 (24–29), n = 2186	0.025
Familial history of CAD	1755/6674 (26.3)	589/2091 (28.2)	0.091
Hypertension	2716/6822 (39.8)	1048/2195 (47.7)	<0.001
Diabetes mellitus	769/6762 (11.4)	373/2185 (17.1)	<0.001
Dyslipidaemia	3205/6576 (48.7)	910/2155 (42.2)	<0.001
Current smoker	2648 (38.7)	839/2183 (38.4)	0.808
Previous myocardial infarction	548/6819 (8.0)	227/2190 (10.4)	0.001
Previous CABG	71/6824 (1.0)	26/2190 (1.2)	0.562
Previous PCI	651 (9.5)	168/2185 (7.7)	0.009
Chronic obstructive pulmonary disease	330/6818 (4.8)	120/2172 (5.5)	0.203
Previous stroke/TIA	241/6818 (3.5)	109 (4.9)	0.003
Peripheral artery disease	277/6816 (4.1)	125/2193 (5.7)	0.001
Permanent pacemaker	42/6816 (0.6)	6/2192 (0.3)	0.055
Presentation			
Presentation as cardiac arrest	138/6683 (2.1)	107 (4.8)	<0.001
Admission to a non-pPCI capable centre	1081 (15.8)	698/2207 (31.6)	<0.001
Managed by MICU	4243 (62.1)	1510 (68.4)	<0.001
ECG on admission			
Q wave	2001/6802 (29.4)	1196/2170 (55.1)	<0.001
Left bundle branch block	124/6795 (1.8)	46 (2.1)	0.438
Anterior myocardial infarction	2800 (40.9)	948 (42.9)	0.099
Treatment delays (min)			
Symptoms-to-first medical contact delay	98 (55–190), *n* = 6329	95 (45–250), *n* = 2149	0.974
Symptoms-to-first medical contact			
Delay > 12 h	204/6329 (3.2)	140/2149 (6.5)	<0.001
First medical contact-to-pPCI delay	95 (76–128), *n* = 6322	144 (90–240)	<0.001
Haemodynamic on admission			
Killip classification			<0.001
I	6277 (91.8)	1858 (84.1)	<0.001
II	418 (6.1)	289 (13.1)	<0.001
III	143 (2.1)	61 (2.8)	0.065
Heart rate (b.p.m.)	75 (63–87), *n* = 6646	77 (65–90)	<0.001
Systolic blood pressure (mmHg)	134 (118–150), *n* = 6698	137 (119–157)	<0.001
Pulse pressure (mmHg)	52 (40–66), *n* = 6675	53 (41–67)	0.052
Blood tests on admission			
Serum creatinine level (μmol/L)	81 (68–94), *n* = 6735	83 (70–100)	<0.001
Glycaemia (mmol/L)	7.6 (6.3–9.2), *n* = 6536	7.7 (6.5–9.6)	0.014
mg/dL	137 (114–166)	139 (117–173)	
Procedural characteristics			
Radial access	3722/5892 (62.8)	1303/1591 (81.9)	<0.001
Infarct-related coronary artery			
Left anterior descending	4005/6837 (41.4)	974 (44.1)	0.026
Left circumflex	1049/6837 (15.3)	303 (13.7)	0.063
Right	2926/6837 (42.8)	915 (41.4)	0.262
Left main	41 (0.6)	12 (0.5)	0.764
Multivessel disease	3228 (47.2)	1137 (51.5)	<0.001
TIMI flow grade 3 before pPCI	1111/6806 (16.3)	304/2182 (13.9)	0.008

Continued

Results

Patients

est (4.8 vs. 2.1%, P
centre (31.6 vs. 15.8%,

ospital
mody-
ystolic
nission
tor

X, USA).

Table 2 Baseline and procedural characteristics associated with the occurrence of cardiogenic shock in univariable analysis in the derivation cohort

Variables	In-hospital CS (*n* = 293)	No in-hospital CS (*n* = 6545)	OR (95% CI)	*P*-value
Baseline characteristics				
Clinical characteristics				
Age (years)	71 (59–80)	62 (52–73)	1.04 (1.03–1.05)	<0.001
Female sex	89 (30.4)	1430 (21.8)	1.56 (1.21–2.02)	0.001
Familial history of CAD	51/277 (18.4)	1704/6397 (26.6)	0.62 (0.46–0.85)	0.003
Hypertension	166/292 (56.8)	2550/6530 (39.1)	2.06 (1.62–2.61)	<0.001
Diabetes mellitus	50/285 (17.5)	719/6477 (11.1)	1.70 (1.24–2.34)	0.001
Previous PCI	40 (13.7)	611 (9.3)	1.54 (1.09–2.17)	0.01
Previous stroke/TIA	25/292 (8.6)	216/6526 (3.3)	2.74 (1.78–4.21)	<0.001
Peripheral artery disease	32/292 (11.0)	245/6399 (3.8)	3.15 (2.14–4.65)	<0.001
Presentation				
Presentation as cardiac arrest	25/284 (8.8)	113/6399 (1.8)	5.37 (3.42–8.43)	<0.001
Admission to a non-pPCI capable centre	59 (20.1)	1022 (15.6)	1.36 (1.02–1.83)	0.04
ECG on admission				
Q wave	110/292 (37.7)	1891/6510 (29.0)	1.48 (1.16–1.88)	0.001
Anterior myocardial infarction	158 (53.9)	2642 (40.4)	1.73 (1.37–2.19)	<0.001
Treatment delays (min)				
First medical contact-to-pPCI delay	114 (90–151)	94 (76–127)	1.003 (1.002–1.005)	<0.001
Haemodynamic on admission				
Killip classification				
I	195 (66.6)	6082 (92.9)	Reference	
II	49 (16.7)	369 (5.6)	4.14 (2.98–5.76)	<0.001
III	49 (16.7)	94 (1.4)	16.26 (11.19–23.62)	<0.001
Heart rate (b.p.m.)	83 (70–100)	75 (63–86)	1.03 (1.02–1.03)	<0.001
Systolic blood pressure (mmHg)	115 (93–131)	135 (120–151)	0.97 (0.97–0.98)	<0.001
Pulse pressure (mmHg)	40 (30–52)	52 (40–67)	0.97 (0.96–0.97)	<0.001
Blood tests on admission				
Glycaemia (mmol/L)	10.0 (7.3–13.3)	7.5 (6.3–9.0)	1.18 (1.15–1.20)	<0.001
Procedural characteristics				
TIMI flow grade 3 before pPCI	28/292 (9.6)	1083/6514 (16.6)	0.53 (0.36–0.79)	0.002
Infarct-related coronary artery				
Left main	11 (3.8)	30 (0.5)	8.47 (4.20–17.08)	0.001
Multivessel disease	173 (59.0)	3055 (46.7)	1.65 (1.30–2.09)	<0.001
TIMI flow grade < 3 after pPCI	68/285 (23.9)	300/6482 (4.6)	6.46 (4.80–8.68)	<0.001

Quantitative data are expressed as median (interquartile range). Categorical variables are expressed as number (percentage).
CABG, coronary artery bypass graft; CAD, coronary artery disease; CS, cardiogenic shock; ECG, electrocardiogram; MICU, mobile intensive care unit; PCI, percutaneous coronary intervention; pPCI, primary percutaneous coronary intervention; TIA, transient ischaemic attack; TIMI, thrombolysis in myocardial infarction.

Predictors of in-hospital cardiogenic shock

Univariable predictors of in-hospital development of CS in the derivation cohort are summarized in *Table 2*.

Eleven predictors, reported in *Figure 2*, were independently associated with in-hospital occurrence of CS by multivariable analysis. The c-statistic of the final model was 0.84 (95% CI: 0.81–0.87) showing high discrimination. Cross-validation predicted a very slight decrease in discriminative ability (c-statistic 0.83, 95% CI 0.80–0.86). The *P*-value of the Hosmer–Lemeshow goodness-of-fit test was 0.28.

ORBI risk score building

Points assigned to each variable of the risk-scoring system were derived from the regression coefficients of the final multivariable model (*Figure 2*). The score was calculated by adding each component and theoretically ranged from 0 to 36. An online calculator is available at www.orbiriskscore.com. In the derivation cohort, the score ranged from 0 to 24. The relationship between the score value and the predicted incidence of in-hospital CS is shown in *Figure 3*. The OR associated with a one point increase of the score was 1.36 (95% CI 1.32–1.40; $P < 0.001$). The c-statistic of the score was 0.84 (95% CI 0.81–0.87) in the derivation cohort. Cross-validation

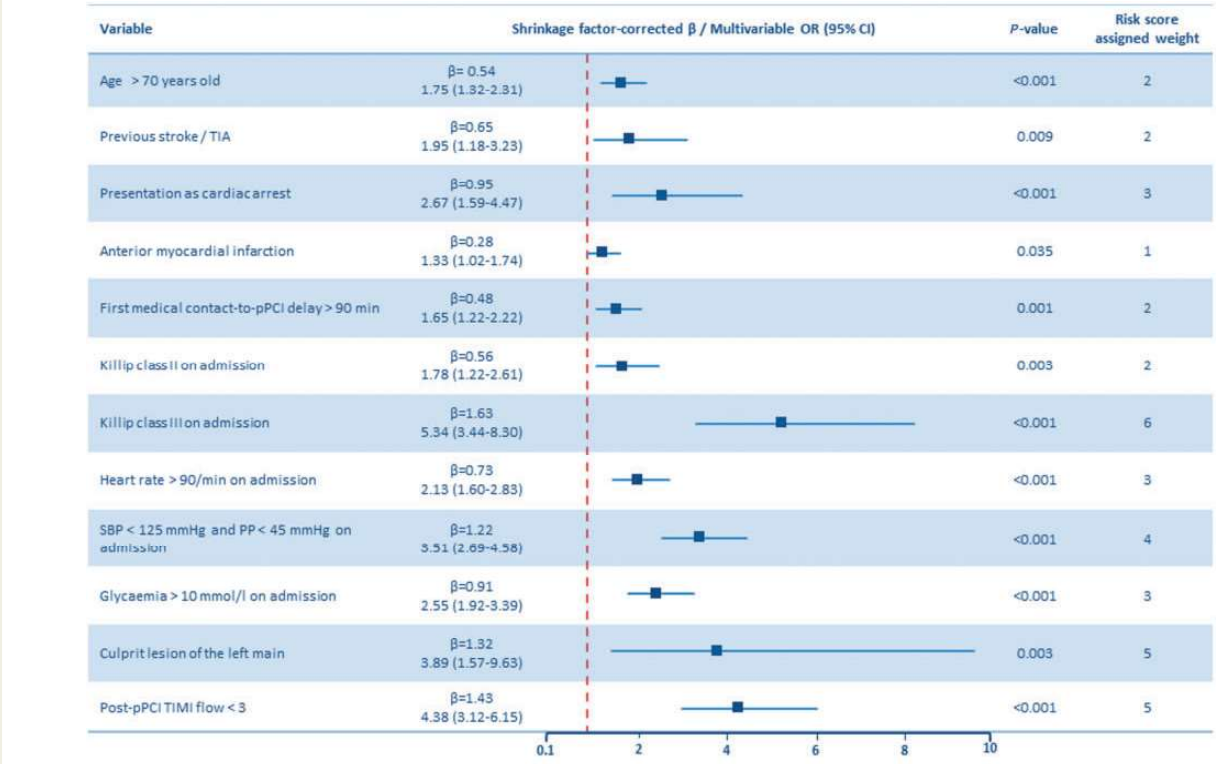


Figure 2 Multivariable predictors of in-hospital cardiogenic shock in the derivation cohort and their respective weights in the Brittany Regional Infarction Observatory risk score. CI, confidence interval; OR, odds ratio; PP, pulse pressure; pPCI, primary percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischaemic attack; TIMI, thrombolysis in myocardial infarction.

demonstrated similar values of 0.84 (95% CI 0.81–0.86). The optimal cut-off identifying a high-risk of in-hospital CS was a score ≥8 (sensitivity 73.6%; specificity 79.5%, positive likelihood ratio 3.59, negative likelihood ratio 0.33). The *P*-value of the Hosmer–Lemeshow test was 0.74. *Figure 4* provides the calibration plot of predicted vs. observed incidence of in-hospital CS in the derivation cohort across deciles of risk score confirming an excellent calibration. Levels of risk were defined according to the predicted incidence of in-hospital CS: low-risk for a score ≤7 corresponding to a predicted incidence <4% (4446 patients, 77.4% of the development cohort), low-to-intermediate risk for a score of 8–10 corresponding to a predicted incidence ≥4% and <10% (777 patients; 13.5%), intermediate-to-high risk for a score of 11 or 12 corresponding to a predicted incidence ≥10% and <15% (247 patients, 4.3%), and high risk for a score ≥13 corresponding to a predicted incidence ≥15% (274 patients, 4.8%). Observed incidences of in-hospital CS according to these cut-offs were 1.3%, 6.6%, 11.7%, and 31.8%, respectively, in the derivation cohort (*Figure 5*).

Score validation

In the validation cohort, the c-statistic of the final model was 0.80 (95% CI 0.77–0.84) with a *P*-value of the Hosmer–Lemeshow test of 0.61. The score showed only weakly reduced discrimination in the validation cohort (c-statistic 0.80, 95% CI 0.77–0.83) with a *P*-value of the Hosmer–Lemeshow test of 0.69. Predicted and observed CS incidences across deciles of risk score for the validation cohort are depicted in *Figure 4*. The distribution of patients of the validation cohort according to their predicted risk was as follows: 68.3% ($n = 1509$) low-risk, 15.0% ($n = 330$) low-to-intermediate risk, 7.0% ($n = 155$) intermediate-to-high risk, and 9.7% ($n = 214$) high-risk. Observed incidence of in-hospital CS according to these increasing levels of risk was 3.1%, 10.6%, 18.1%, and 34.1%, respectively, in the validation cohort (*Figure 5*). The distributions of patients according to risk score and the occurrence of in-hospital CS in the derivation and validation cohorts are shown in *Supplementary material online, Figure S1*.

The prediction model was further evaluated by incorporating clinical consequences throughout the probability ranges, by the use of a decision curve analysis (*Figure 6*). The results demonstrated that for relevant decision thresholds, the ORBI risk score model provided a substantial net clinical benefit compared with a model including only admission haemodynamic variables (Killip Class II or III, heart rate > 90/min, combination of systolic blood pressure < 125 mmHg, and pulse pressure < 45 mmHg) and a model using the admission shock index. For a decision threshold of 5% of in-hospital CS risk, compared with these models, the ORBI risk score would identify ∼10 additional cases, without identifying any additional false positive, in a population of 1000 patients with a 4.3% incidence of in-hospital CS.

Discussion

The present study is, to the best of our knowledge, the first to provide a readily useable scoring system to identify STEMI patients with

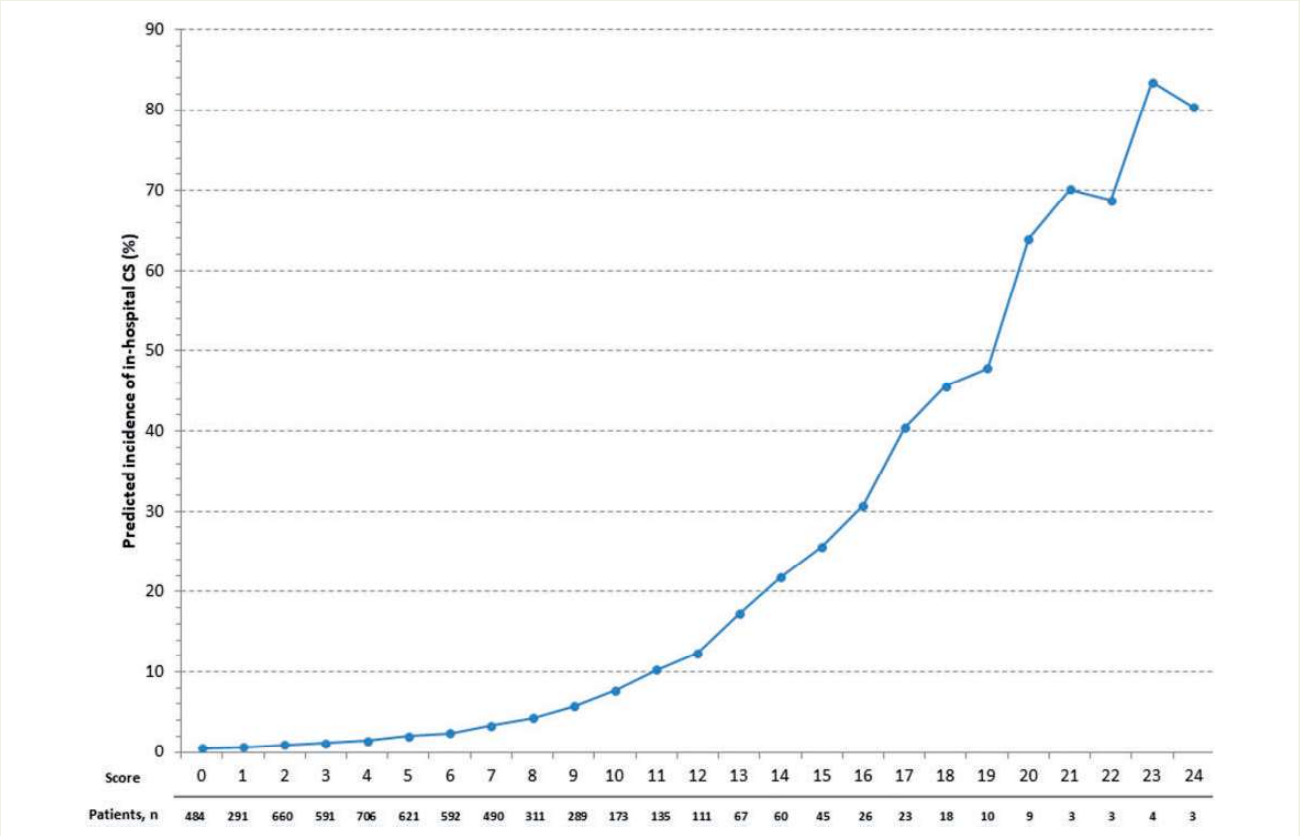


Figure 3 Relationship between the score value and the predicted incidence of in-hospital cardiogenic shock. CS, cardiogenic shock.

impending CS following pPCI. In this large homogeneous cohort of pPCI-treated STEMI patients without CS on admission, 11 routinely collected variables, 8 patient-related, and 3 procedure-related, available in the catheterization laboratory, independently predicted the development of in-hospital CS post-pPCI. The ORBI risk score (*Take home figure*), including these variables, showed good predictive ability and calibration across the significantly different populations of the derivation and validation cohorts, further supporting the quality of the external validation. Being based on simple categorical parameters, the score can be easily calculated in routine clinical practice. This score could be useful in the selection of high-risk patients, especially in the setting of future randomized trials designed to provide a tailored aggressive management to the so-called 'pre-shock' patients.

Although, in the setting of STEMI, acute heart failure remains one of the strongest predictors of short-term mortality in the contemporary era, regardless of its timing or severity, this relationship is mainly driven by patients experiencing CS.[2] In a recent series of 6282 pPCI-treated patients, we demonstrated an overall rate of approximately 8% of STEMI-related CS with 54% of cases occurring after hospital admission.[2] Interestingly, in a decade-long evaluation of STEMI patients included at 11 centres in Massachusetts between 2001 and 2011, Goldberg *et al.*[22] demonstrated a relatively unchanged 4% incidence of in-hospital development of CS. Notwithstanding the decline of case-fatality rate observed over the past decades, it is fair to say that the 40% short-term mortality rate still observed in recent series[6,9] remains unacceptably high and testifies to the unresolved clinical challenge posed by CS. In keeping with this point, it should be highlighted that the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial, which spurred the widespread use of early reperfusion, (i.e. the last successful innovation in ischaemic CS management), was published more than 15 years ago.[18] Since then, the systematic use of IABP, compared with early revascularization alone, failed to improve systemic inflammation, tissue oxygenation, and survival in ischaemic CS patients.[9] Moreover, there is currently no evidence that more elaborative left ventricular assist devices such as the Impella (PL2.5 or CP, Abiomed, Danvers, MA, USA) or the TandemHeart™ (CardiacAssist Inc., Pittsburgh, PA, USA), provide clinical benefits above and beyond an IABP, other than providing greater haemodynamic support.[11,23] Recently, Thiele *et al.*[8] randomized 706 patients with acute myocardial infarction-related CS to immediate multivessel or culprit lesion-only pPCI. Patients in the immediate multivessel pPCI group exhibited a higher rate of the 30-day primary composite endpoint of all-cause death and renal replacement therapy, including a significant increase in 30-day mortality. The CULPRIT-SHOCK trial, adding to the long list of negative trials in the CS setting, will therefore likely have a major clinical impact as it contradicts latest European Guidelines which gave non-culprit lesion pPCI during the index procedure a IIaC recommendation.[24] A pharmacological strategy aimed to target circulatory failure,

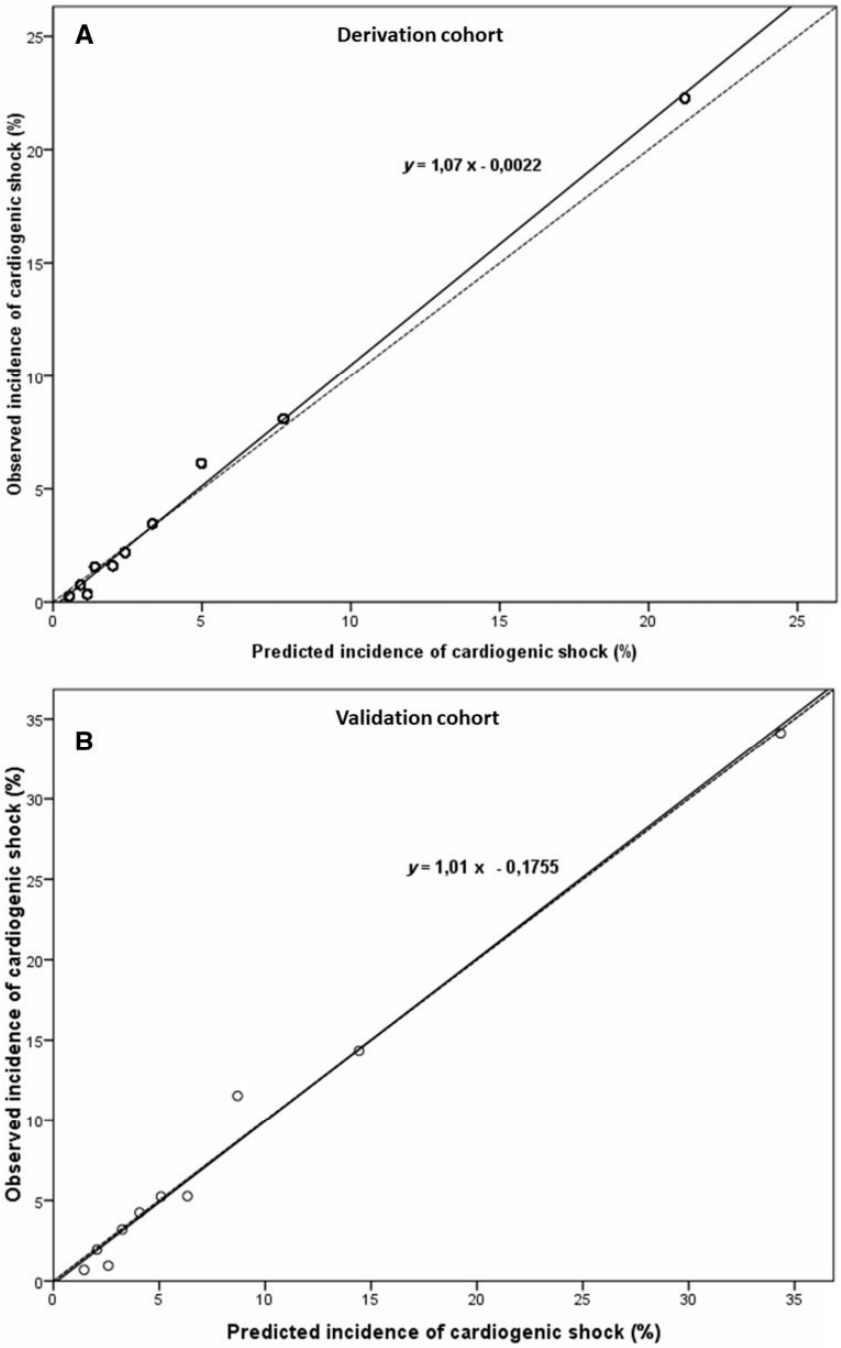


Figure 4 Calibration plots. Calibration plots showing the predicted probability vs. observed incidence of in-hospital cardiogenic shock in the derivation and validation cohorts. The diagonal dotted line represents the perfect calibration ($y = x$; curve with a slope of 1 and an intercept of 0).

such as nitric oxide synthase inhibition, evaluated in the Tilarginine Acetate Injection in a Randomized International Study in Unstable MI Patients With Cardiogenic Shock (TRIUMPH) trial, also showed no meaningful short-term clinical improvement in patients with ischaemic CS despite an open infarct artery.[25] Collectively, these data suggest that strategies tackling a single aspect of the complex, deleterious, physiopathological spiral underlying CS may be 'too little, too late' to achieve a sustained reversal of this vicious circle, especially when multiorgan dysfunction syndrome has developed.[12,23]

In clinical practice, CS encompasses a spectrum ranging from 'pre-shock' to overt severe refractory shock.[26] Identifying the former state is extremely appealing as it may reduce short-term mortality by preventing progression to overt CS by promptly initiating aggressive management strategies. Nevertheless, albeit widely used, this term has no generally accepted definition and the current literature is

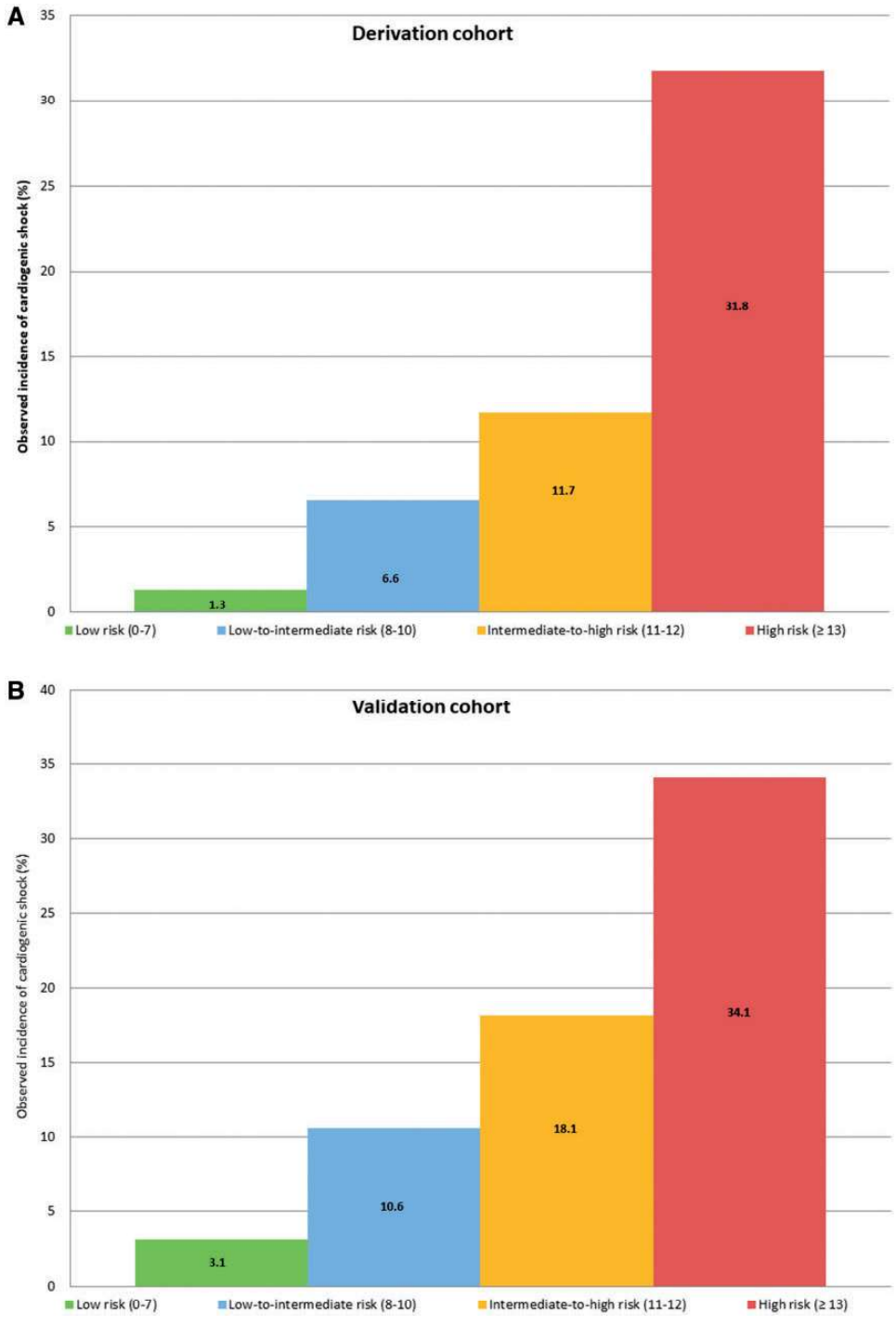


Figure 5 Observed incidence of cardiogenic shock. Observed incidence of cardiogenic shock according to categories of the Brittany Regional Infarction Observatory risk score in the derivation and validation cohorts.

elusive regarding factors that may help delineate this high-risk entity.[26] Recent analyses identified older age, diabetes mellitus, stroke, treatment delays, anterior STEMI, heart rate, systolic blood pressure, cardiac arrest, elevated glycaemia, and impaired renal function to associate with the development of in-hospital CS.[22,27] Moreover, as in the present model, age, prior stroke, admission glycaemia >10.6 mmol/L, and post-pPCI thrombolysis in myocardial infarction (TIMI) flow grade <3 were also included in the recently published IABP-SHOCK II risk score.[28] This score was designed to predict 30-day mortality in acute myocardial infarction-related CS patients, demonstrating good predictive ability (with c-statistic of 0.79 and 0.73 in its derivation and validation cohorts, respectively). In addition to the

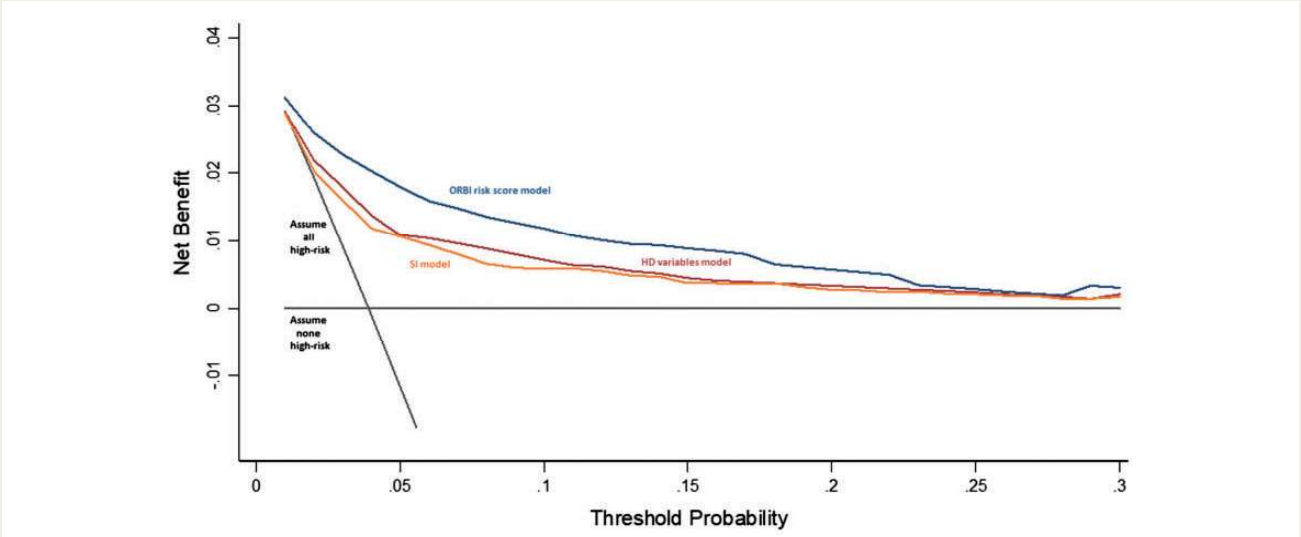


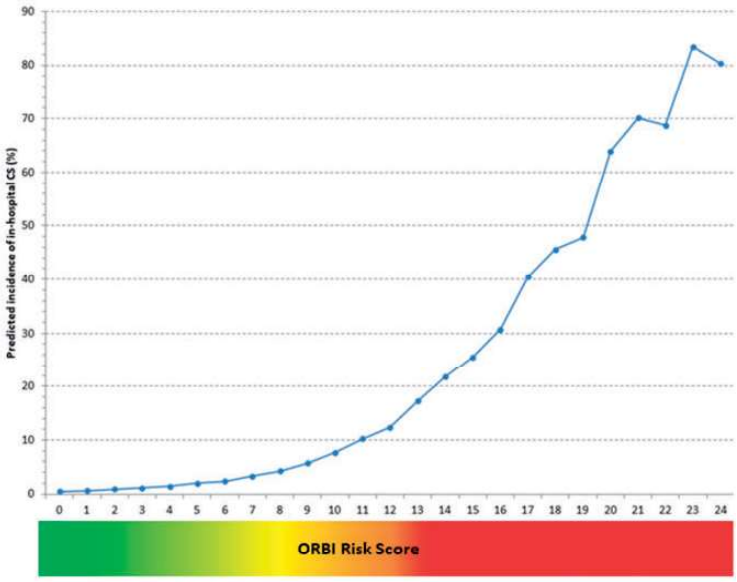
Figure 6 Decision curve analysis. Net benefit of using a model to predict in-hospital cardiogenic shock development compared with strategies of 'assuming all' or 'assuming none' patients would be at high-risk for different decision thresholds is shown. The Brittany Regional Infarction Observatory risk score (blue) demonstrated improved benefit compared with a model based only on haemodynamic variables on admission (red) and a model based on the admission shock index (orange).

above-mentioned parameters, it also includes admission levels of creatinine >1.5 mg/dL and blood lactate > 5 mmol/L. The former parameter was knowingly excluded from our multivariable model as it may not be available following the pPCI procedure yet still demonstrated univariable association with shock development in the present study. Blood lactate was not routinely recorded in our cohorts and therefore could not be tested as a potential predictor of CS, explaining the difference between the IABP and ORBI risk scores. Finally, in a large German registry including 1333 ischaemic CS patients,[29] older age, culprit lesion of the left main, post-pPCI TIMI flow <3 and longer delays between symptoms, and pPCI were also predictors of in-hospital mortality which reinforces the prognostic impact of factors identified in the present analysis.

The ORBI risk score presented in this study has several strengths. First, it has been developed from a large homogeneous population of STEMI patients treated by pPCI, which essentially represents contemporary practices. Second, it includes dichotomized variables that are easily collected and available in the catheterization laboratory, and it can be quickly calculated in routine practice as it does not require complex processing of the variables. Third, as previously discussed, it efficiently addresses a major unmet clinical need, refining the identification of patients at high-risk of CS development at the end of a pPCI procedure which may be the most suitable time to initiate early adjunctive therapies. Fourth, it has been validated in an external cohort exhibiting significant differences in the baseline characteristics of included patients compared with the derivation cohort, further supporting the validity and reliability of this risk score over a large span of baseline in-hospital CS risk. And fifth, it has demonstrated superior clinical benefit compared with models based on haemodynamic variables or the shock index which approximate the intuitive bedside assessment performed by clinicians upon admission of these STEMI patients.

A single risk score is unlikely to include all relevant parameters allowing risk estimation and as such will not substitute for a thorough clinical evaluation. However, the ORBI risk score provides a simple tool to help decision making, which may have several clinical implications. The higher risk patients may benefit from an early transfer to an intensive cardiac care unit with experience in the management of CS, especially in mechanical circulatory support. Moreover, avoidance of the use of β-blockers and angiotensin-converting enzyme inhibitors in the very early management of high-risk patients may prevent iatrogenic shock. In recent years, complete revascularization demonstrated improved clinical outcomes over culprit lesion-only revascularization in haemodynamically stable STEMI patients.[30] However, the optimal timing of complete revascularization remains unknown. Conceivably, by alleviating the ischaemic burden of non-infarct territories, immediate complete revascularization may prevent the occurrence of overt CS among high-risk patients. However, as previously stated, this strategy resulted in worse short-term outcomes, including 30-day mortality, compared with culprit lesion-only pPCI when CS-driven systemic physiopathological alterations already started.[8] Based on recent randomized trials in haemodynamically stable patients, a strategy of routine PCI of non-infarct-related arteries lesions before hospital discharge (thus including during the index procedure) has recently been given a Class IIaA recommendations in the latest European guidelines.[24] Although the systematic use of IABP has yet to show proven benefit in an all-comers STEMI population, evidence from a small CRISP-AMI sub-study suggest it might have positive effect in selected high-risk patients with persistent ischaemia.[31] Therefore, the use of devices with low rates of complications such as IABP to allow the severely ischaemic myocardium to recover may be evaluated in high-risk patients as identified by the ORBI risk score. Finally, pharmacological strategies targeting the systemic inflammatory response syndrome promoting overt CS[1,12,25] may also be guided by the present risk score.

Variable	Points
Age >70 years old	2
Previous stroke / TIA	2
Presentation as cardiac arrest	3
Anterior myocardial infarction	1
First medical contact-to-pPCI delay >90 min	2
Killip class II on admission	2
Killip class III on admission	6
Heart rate >90/min on admission	3
SBP <125 mmHg and PP <45 mmHg on admission	4
Glycaemia >10 mmol/l on admission	3
Culprit lesion of the left main	5
Post-pPCI TIMI flow <3	5



Risk categories

Category	Score	Observed incidence of CS
Low	0-7	1.3
Low-to-intermediate	8-10	6.6
Intermediate-to-high	11-12	11.7
High	≥ 13	31.8

Take home figure The Brittany Regional Infarction Observatory risk score model. The Brittany Regional Infarction Observatory risk score was created using stepwise multivariable regression to predict the development of in-hospital cardiogenic shock in patients with ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention. Score weights were determined by rounding the respective parameters adjusted odds ratio. The score, theoretically ranging from 0 to 36 points, was divided in risk category according to the predicted incidence of cardiogenic shock: low: 0 to 7 points; low-to-intermediate: 8 to 10 points; intermediate-to-high: 11 or 12 points; high: 13 or more points. Within the derivation cohort, 4446 patients (77.4%) were classified low-risk, 777 (13.5%) low-to-intermediate risk, 247 (4.3%) intermediate-to-high risk, and 274 (4.8%) high risk. PP, pulse pressure; pPCI, primary percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischaemic attack; TIMI, thrombolysis in myocardial infarction.

Study limitations

The diagnosis of CS was not adjudicated but made locally by the treating physician mainly by clinical judgement without pre-specified strict haemodynamic or echocardiographic criteria. However, the incidences and case-fatality rates of in-hospital CS reported in our derivation and validation cohorts are consistent with the current literature and make under- or over-reporting of CS unlikely. Moreover, despite this somewhat 'subjective' reporting of CS, the score performed well in both cohorts highlighting its predictive ability. Certain biological parameters of prognostic value in the STEMI setting, such as white blood cell count or serum lactate levels, were not available for testing in our database. Furthermore, the TIMI flow grade was not assessed by a central core laboratory which may lead to discrepancies between operators and overestimation of this reperfusion indicator.[32] Thus, the true predictive impact of an 'adequately' assessed TIMI flow grade might differ from the odds identified in the present study. However, the ORBI risk score was designed from routine practice for routine practice. Therefore, the investigator-reported TIMI flow grade used in this study, more accurately depicting real life, is rather an asset in this setting. Given the good predictive performances of the score in our two large cohorts of STEMI patients with multiple operators, it also supports the reliability of the risk-scoring system. Finally, it should be highlighted that more sophisticated prediction models such as those involving machine learning,[33] may have provided improved model performance however regression methods have the advantage of allowing an easy conversion of the model coefficients into a point-based score for routine practice use.

Conclusion

The ORBI risk score is a simple and efficient tool that may be calculated at the end of a pPCI procedure in routine practice to identify patients with a high-risk of in-hospital development of CS. It might provide valuable assistance to risk-stratify patients and facilitate clinical decision making as well as patients' selection for future prospective randomized trials.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

The authors are indebted to all physicians and clinical research assistants that ensured data collection and monitoring of the ORBI and RICO registries. They also want to thank Emmanuel Oger for sharing his statistical experience.

Funding

No extra-mural funding supported the present work. ORBI is supported by a grant from Daiichi-Sankyo for data collection and management. RICO was supported by the University Hospital of Dijon, the Association de Cardiologie de Bourgogne, and by grants from the Agence Régionale de Santé (ARS) de Bourgogne-Franche Comté, French Ministry of Research, Institut National de la Santé et de la Recherche Médicale (INSERM), and from the Conseil Régional de Bourgogne-Franche Comté.

Conflict of interest: V.A. received fellowship support from the Fédération Française de Cardiologie and research grants from Abbott, Edwards Lifescience, Medtronic, Biosensors, Terumo, and Boston Scientific. All other authors have nothing to declare.

References

1. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. *Circulation* 2008;**117**:686–697.
2. Auffret V, Leurent G, Gilard M, Hacot JP, Filippi E, Delaunay R, Rialan A, Rouault G, Druelles P, Castellant P, Coudert I, Boulanger B, Treuil J, Bot E, Bedossa M, Boulmier D, Le Guellec M, Donal E, Le Breton H. Incidence, timing, predictors and impact of acute heart failure complicating ST-segment elevation myocardial infarction in patients treated by primary percutaneous coronary intervention. *Int J Cardiol* 2016;**221**:433–442.
3. Kunadian V, Qiu W, Ludman P, Redwood S, Curzen N, Stables R, Gunn J, Gershlick A. Outcomes in patients with cardiogenic shock following percutaneous coronary intervention in the contemporary era: an analysis from the BCIS database (British Cardiovascular Intervention Society). *JACC Cardiovasc Interv* 2014;**7**:1374–1385.
4. Babaev A, Frederick PD, Pasta DJ, Every N, Sichrovsky T, Hochman JS. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *Jama* 2005;**294**:448–454.
5. Desta L, Jernberg T, Lofman I, Hofman-Bang C, Hagerman I, Spaak J, Persson H. Incidence, temporal trends, and prognostic impact of heart failure complicating acute myocardial infarction. The SWEDEHEART Registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies): a study of 199, 851 patients admitted with index acute myocardial infarctions, 1996 to 2008. *JACC Heart Fail* 2015;**3**:234. 42.
6. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. *Eur Heart J* 2015;**36**:1223–1230.
7. Thiele H, Allam B, Chatellier G, Schuler G, Lafont A. Shock in acute myocardial infarction: the Cape Horn for trials? *Eur Heart J* 2010;**31**:1828–1835.
8. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, Nordbeck P, Geisler T, Landmesser U, Skurk C, Fach A, Lapp H, Piek JJ, Noc M, Goslar T, Felix SB, Maier LS, Stepinska J, Oldroyd K, Serpytis P, Montalescot G, Barthelemy O, Huber K, Windecker S, Savonitto S, Torremante P, Vrints C, Schneider S, Desch S, Zeymer U. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med* 2017;**377**:2419–2432.
9. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Bohm M, Ebelt H, Schneider S, Schuler G, Werdan K. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;**367**:1287–1296.
10. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, de Waha A, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Lauer B, Bohm M, Ebelt H, Schneider S, Werdan K, Schuler G. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet* 2013;**382**:1638–1645.
11. Ouweneel DM, Eriksen E, Sjauw KD, van Dongen IM, Hirsch A, Packer EJ, Vis MM, Wykrzykowska JJ, Koch KT, Baan J, de Winter RJ, Piek JJ, Lagrand WK, de Mol BA, Tijssen JG, Henriques JP. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol* 2017;**69**:278–287.
12. Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. *Circulation* 2003;**107**:2998–3002.
13. Patel MR, Smalling RW, Thiele H, Barnhart HX, Zhou Y, Chandra P, Chew D, Cohen M, French J, Perera D, Ohman EM. Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial. *Jama* 2011;**306**:1329–1337.
14. Cung TT, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, Bonnefoy-Cudraz E, Guerin P, Elbaz M, Delarche N, Coste P, Vanzetto G, Metge M, Aupetit JF, Jouve B, Motreff P, Tron C, Labeque JN, Steg PG, Cottin Y, Range G, Clerc J, Claeys MJ, Coussement P, Prunier F, Moulin F, Roth O, Belle L, Dubois P, Barragan P, Gilard M, Piot C, Colin P, De Poli F, Morice MC, Ider O, Dubois-Rande JL, Unterseeh T, Le Breton H, Beard T, Blanchard D, Grollier G, Malquarti V, Staat P, Sudre A, Elmer E, Hansson MJ, Bergerot C, Boussaha I, Jossan C, Derumeaux G, Mewton N, Ovize M. Cyclosporine before PCI in patients with acute myocardial infarction. *N Engl J Med* 2015;**373**:1021–1031.
15. Auffret V, Loirat A, Leurent G, Martins RP, Filippi E, Coudert I, Hacot JP, Gilard M, Castellant P, Rialan A, Delaunay R, Rouault G, Druelles P, Boulanger B, Treuil J, Avez B, Bedossa M, Boulmier D, Le Guellec M, Daubert JC, Le Breton H. High-degree atrioventricular block complicating ST segment elevation myocardial infarction in the contemporary era. *Heart* 2016;**102**:40–49.
16. Zeller M, Cottin Y, Brindisi MC, Dentan G, Laurent Y, Janin-Manificat L, L'Huillier I, Beer JC, Touzery C, Makki H, Verges B, Wolf JE. Impaired fasting glucose and cardiogenic shock in patients with acute myocardial infarction. *Eur Heart J* 2004;**25**:308–312.
17. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BR, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Gabriel Steg P, Wijns W, Bassand J-P, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon J-L, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–2567.
18. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med* 1999;**341**:625–634.
19. Rubin D. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley and Sons; 1987.
20. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J* 2014;**35**:1925–1931.
21. Huang B, Yang Y, Zhu J, Liang Y, Tan H, Yu L, Gao X, Li J. Usefulness of the admission shock index for predicting short-term outcomes in patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 2014;**114**:1315–1321.
22. Goldberg RJ, Makam RC, Yarzebski J, McManus DD, Lessard D, Gore JM. Decade-long trends (2001-2011) in the incidence and hospital death rates associated with the in-hospital development of cardiogenic shock after acute myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2016;**9**:117–125.
23. Werdan K, Gielen S, Ebelt H, Hochman JS. Mechanical circulatory support in cardiogenic shock. *Eur Heart J* 2014;**35**:156–167.
24. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
25. Alexander JH, Reynolds HR, Stebbins AL, Dzavik V, Harrington RA, Van de Werf F, Hochman JS. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. *Jama* 2007;**297**:1657–1666.

26. Delmas C, Leurent G, Lamblin N, Bonnefoy E, Roubille F. Cardiogenic shock management: still a challenge and a need for large-registry data. *Arch Cardiovasc Dis* 2017;**110**:433–438.
27. Obling L, Frydland M, Hansen R, Møller-Helgestad OK, Lindholm MG, Holmvang L, Ravn HB, Wiberg S, Thomsen JH, Jensen LO, Kjærgaard J, Møller JE, Hassager C. Risk factors of late cardiogenic shock and mortality in ST-segment elevation myocardial infarction patients. *Eur Heart J Acute Cardiovasc Care* 2018;**7**:7. 2048872617706503.
28. Poss J, Koster J, Fuernau G, Eitel I, de Waha S, Ouarrak T, Lassus J, Harjola VP, Zeymer U, Thiele H, Desch S. Risk stratification for patients in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol* 2017;**69**:1913–1920.
29. Zeymer U, Vogt A, Zahn R, Weber MA, Tebbe U, Gottwik M, Bonzel T, Senges J, Neuhaus KL. Predictors of in-hospital mortality in 1333 patients with acute myocardial infarction complicated by cardiogenic shock treated with primary percutaneous coronary intervention (PCI); Results of the primary PCI registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte (ALKK). *Eur Heart J* 2004;**25**:322–328.
30. Elgendy IY, Mahmoud AN, Kumbhani DJ, Bhatt DL, Bavry AA. Complete or culprit-only revascularization for patients with multivessel coronary artery disease undergoing percutaneous coronary intervention: a pairwise and network meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2017;**10**:315–324.
31. van Nunen LX, van 'T Veer M, Schampaert S, Rutten MCM, van de Vosse FN, Patel MR, Pijls NHJ. Intra-aortic balloon counterpulsation reduces mortality in large anterior myocardial infarction complicated by persistent ischaemia: a CRISP-AMI substudy. *EuroIntervention* 2015;**11**:286–292.
32. Alhadramy O, Westerhout CM, Brener SJ, Granger CB, Armstrong PW. Is visual interpretation of coronary epicardial flow reliable in patients with ST-elevation myocardial infarction undergoing primary angioplasty? Insights from the angiographic substudy of the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial. *Am Heart J* 2010;**159**:899–904.
33. Goldstein BA, Navar AM, Carter RE. Moving beyond regression techniques in cardiovascular risk prediction: applying machine learning to address analytic challenges. *Eur Heart J* 2017;**38**:1805–1814.