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Simultaneous Measurement of Cardiac Troponin I, B-type Natriuretic Peptide, and C-reactive Protein for the Prediction of Long-term Cardiac Outcome after Cardiac Surgery

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Background: **Simultaneous assessment of cardiac troponin I, B-type natriuretic peptide, and C-reactive protein has been found to provide unique prognostic information in acute coronary syndromes. The current study addressed the prognostic implication of a multiple-marker approach in cardiac surgery.**

Methods: **Two hundred twenty-four patients undergoing cardiac surgery were included and followed up within 12 months after surgery. Serial blood samples were drawn in all patients the day before surgery, at the end of surgery, and 6, 24, and 120 h after surgery. Major adverse cardiac events within 12 months after surgery were chosen as study endpoints and were defined as malignant ventricular arrhythmia, myocardial infarction, congestive heart failure, the need for myocardial revascularization, and/or death from cardiac cause. Predictive ability of each cardiac biomarker was assessed using logistic regression.**

Results: **Accuracies of C-reactive protein, cardiac troponin I, and B-type natriuretic peptide, considered as continuous variables, to predict the occurrence of major adverse cardiac events were limited (area under receiver operating characteristic curve: 0.54 [0.47–0.60], $P = 0.42$; 0.62 [0.55–0.68], $P = 0.01$; and 0.68 [0.61–0.74], $P < 0.001$, respectively). When biomarkers were considered as 75% specificity dichotomized variables, elevated C-reactive protein (> 180 mg/l), cardiac troponin I (> 3.5 ng/ml), and B-type natriuretic peptide (> 880 pg/ml) were independent predictors of major adverse cardiac events (odds ratio: 2.14 [1.03-4.49], $P = 0.043$; 2.37 [1.25–5.64], $P = 0.011$; and 2.65 [1.16–4.85], $P = 0.018$, respectively) in a multivariate model including the European System for Cardiac Operative Risk Evaluation score.**

Conclusions: **Simultaneous measurement of cardiac troponin I, B-type natriuretic peptide, and C-reactive protein improves the risk assessment of long-term adverse cardiac outcome after cardiac surgery.**

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MAJOR cardiac complications after cardiac surgery with cardiopulmonary bypass (CPB) can substantially affect outcome.[1] Early diagnosis and risk stratification are therefore important issues to develop therapeutic goals that could improve patient care. Therefore, reliable biologic markers as predictors of the occurrence of short- and long-term cardiac complications would be helpful in routine clinical practice.

Cardiac troponin I (cTnI) is found in cardiac myocytes and is released when myocardial damage occurs, irrespective of the mechanism.[2] The short-term prognostic value of an elevated peak serum cTnI is well established after cardiac surgery[3] and improves the ability to predict in-hospital mortality in comparison with preoperative risk scores alone.[4] The accuracy of cTnI in predicting adverse outcome, however, may be different among different cardiac procedures, being less in valve than in coronary surgery.[5] Moreover, the long-term prognostic value of postoperative cTnI release remains controversial.[6,7] B-type natriuretic peptide (BNP) is released from ventricular cardiac myocytes in response to increases in wall tension and stretch.[8] BNP measurement has recently emerged as being valuable in the cardiac surgical setting,[9] and several studies reported the prognostic value of preoperative BNP concentrations.[10,11] The association between postoperative BNP release and long-term outcome after cardiac surgery, however, remains uncertain.[9,12] C-reactive protein (CRP) is a nonspecific marker of inflammation routinely used at the bedside. Preoperative measurement of CRP has been associated with postoperative cardiac risk after coronary artery bypass grafting.[13,14] Importantly, these three biomarkers assess different pathophysiologic mechanisms: cTnI indicates myocardial necrosis, BNP is elevated in response to left ventricular overload, and CRP is a nonspecific marker of inflammation. Therefore, even if each biomarker may confer different relative risks for individual components of composite adverse cardiac outcomes, simultaneous assessment of all three biomarkers could provide complementary information and enable clinicians to better stratify postoperative risk. However, no data are available regarding potential usefulness in clinical practice of an integrating approach of measuring multiple cardiac biomarkers for the prediction of short- and long-term outcomes after cardiac surgery.

The objective of the current observational study conducted in adult patients undergoing elective cardiac sur-

gery with CPB was to evaluate the prognostic information provided by a multiple-marker approach, the hypothesis tested being that simultaneous measurement of serum cTnI, BNP, and CRP in combination would enable powerful prediction of cardiac risk up to 12 months after cardiac surgery and provide additional information compared with a traditional approach using each biomarker alone.

Materials and Methods

Patient Population

Consecutive adult patients undergoing cardiac surgery with CPB were enrolled prospectively into the study from October 2005 to April 2006 at the Saint-Martin Hospital (Caen, France). Institutional approval was obtained from the Ethical Committee (Comité pour la Protection des Personnes Pitié-Salpêtrière, Paris, France). Waived written informed consent was authorized because the study was solely observational, and preoperative and postoperative cTnI, BNP, and CRP measurements were systematically performed from a blood sample withdrawn for other routine blood tests, during routine care of patients that conformed to standard procedures currently used at our institution. Inclusion criteria were elective cardiac surgical procedures with CPB: coronary artery bypass grafting, aortic or mitral valve replacement, and combined cardiac surgery (coronary artery bypass grafting plus aortic or mitral valve replacement). The following categories of patients were excluded: emergency surgery (< 24 h), mitral valvuloplasty, and other complex or unusual cardiac surgical procedures.

Perioperative Management

All patients were premedicated with oral lorazepam (2 mg the evening before surgery and on the morning of surgery). β-Blocking agents and statins were given until the day of surgery in chronically treated patients. Oral antiplatelet agents were stopped within 7–10 days before surgery and were replaced by oral flurbiprofen (50 mg twice) until the day before surgery. Standardized total intravenous anesthesia (target-controlled propofol infusion, remifentanil, and pancuronium bromide) and monitoring techniques (five-lead electrocardiogram, invasive arterial blood pressure, and central venous pressure) were used in all patients and complied with routine practice at our hospital.[5,6] Antifibrinolytic therapy (tranexamic acid, 15 mg/kg twice) was routinely administered. CPB was performed under normothermia (> 35.5°C) in all types of surgery, and myocardial protection was achieved by intermittent anterograde or combined (anterograde plus retrograde) warm blood cardioplegia, as previously described.[5,6] Boluses of ephedrine and/or phenylephrine were intraoperatively given as necessary to maintain mean arterial pressure between 50 and 80 mmHg. The heart was defibrillated after aortic unclamping if sinus rhythm did not resume spontaneously. After termination of CPB, catecholamines were used when necessary, at the discretion of the attending anesthesiologist. All patients were admitted postoperatively into the cardiac intensive care unit for at least 48 h and were assessed for tracheal extubation within 1–8 h of arrival in the intensive care unit. Standard postoperative care included blood glucose control (< 8 mM), intravenous heparin (200 U/kg) in patients with valve disease, and aspirin (300 mg, oral or intravenous) associated with low-molecular-weight heparin (nadroparin, 2,850 U anti-Xa, subcutaneous; Fraxiparine®; Sanofi-Synthelabo, Paris, France) in patients with coronary artery disease, beginning 6 h after surgery in the absence of significant mediastinal bleeding (> 50 ml/h). β-Blocking agents and statins were given as soon as possible postoperatively in chronically treated patients.[15,16] Postoperative care was delivered by anesthesiologists in the intensive care unit and by cardiac surgeons in the ward. All of them were blinded for cardiac biomarkers levels, except for the 24-h cTnI measurement, which has been routinely used at the bedside for several years at our institution. Preoperative, intraoperative, and postoperative variables were collected for all patients.

Measurements of cTnI, BNP, and CRP Concentrations

Serial blood samples were drawn into dry tubes the day before surgery, at the end of surgery, and 6, 24, and 120 h after surgery. cTnI, BNP, and CRP measurements at these five time points were systematically performed from blood samples withdrawn for other routine blood tests. A technician who was unaware of the clinical and electrocardiogram data performed assays. cTnI was analyzed with a sensitive and highly specific immunoenzymometric assay (AxSYM Troponin-I *ADV* assay; Abbott Laboratories, Rungis, France) that detects both free and complex bound troponin. The assay allowed the detection of cTnI within the range of 0.02–23 ng/ml with appropriate dilutions. Values greater than 0.04 ng/ml were considered abnormal. The within-run coefficient of variation was 6%, and the between-run coefficient of variation was 11%. BNP was analyzed with a sensitive and highly specific immunoenzymometric assay (AxSYM BNP MEIA assay; Abbott Laboratories). The assay allowed the detection of BNP within the range of 0–20,000 pg/ml with appropriate dilutions. Values greater than 100 pg/ml were considered abnormal. The within-run coefficient of variation was 6%, and the between-run coefficient of variation was 9%. CRP was analyzed with a turbidimetric method (SYNCHRON CX C-RP; Beckman Coulter Inc., Roissy, France). The assay allowed the detection of CRP within the range of 2.0–500.0 mg/l with appropriate dilutions. Values greater

than 6.0 mg/l were considered abnormal. The within-run coefficient of variation was 5%, and the between-run coefficient of variation was 10%.

Clinical Outcome and Follow-up

Nonfatal major cardiac events and all causes of death were recorded postoperatively during in-hospital stay and within 12 months after hospital discharge. The survivors after hospital discharge or their relatives as well as their general practitioner and/or cardiologist were subsequently contacted by telephone for a 1-yr follow-up interview to obtain information.

Nonfatal major cardiac events included (1) malignant ventricular arrhythmia, defined as any sustained ventricular arrhythmia requiring treatment that occurred during the postoperative period and/or within 12 months after surgery; (2) myocardial infarction, defined as the appearance on 12-lead electrocardiogram recordings of new Q waves of more than 0.04 s and 1 mm deep or a reduction in R waves of more than 25% in at least two continuous leads of the same vascular territory at any time within 12 months after surgery, as previously described[5,6]; (3) cardiac dysfunction, defined as clinical signs of congestive heart failure (fluid retention, oliguria, basilar rales, persistent chest infiltration requiring diuretic agents) and/or hemodynamic instability requiring inotropic support for at least 24 h and/or a decrease of 20% or greater in preoperative-to-postoperative left ventricular ejection fraction during the postoperative period and as clinical signs of congestive heart failure requiring rehospitalization within 12 months after surgery; and (4) the need for new revascularization defined as percutaneous coronary angioplasty and/or coronary artery bypass grafting within 12 months after surgery.

In case of death, all information available (hospital chart, death certificate) was used to classify death as from a cardiac cause (heart failure, myocardial infarction, ventricular arrhythmia) or not (other causes). Sudden death was considered as death from a cardiac cause.

Endpoints

Major adverse cardiac events (MACEs) during in-hospital stay and within 12 months after surgery were chosen as study endpoints and defined as one of the following: malignant ventricular arrhythmia, myocardial infarction, cardiac dysfunction, the need for myocardial revascularization, and death from cardiac cause as defined in the previous paragraph. The presence or absence of MACEs was judged by two experts who were blinded to concentrations of cardiac biomarkers. In the case of disagreement, a third blinded expert participated in a discussion with the first two, and a consensus was reached.

Statistical Analysis

Data are expressed as mean ± SD, median [extremes] for nonnormally distributed variables (Kolmogorov–Smirnov test), or number and percentage as appropriate. Continuous variables were analyzed with the unpaired Student *t* and Mann–Whitney U tests, according to their distribution. Categorical variables were compared by the Fisher exact method.

To assess the accuracy of postoperative peak values of cTnI, BNP, and CRP in predicting MACEs, we determined the receiver operating characteristic (ROC) curves and calculated the areas under the ROC curves and their 95% confidence intervals. Comparison of areas under the ROC curve was performed using a nonparametric technique, as previously described.[17] The ROC curves were also used to determine the best thresholds for cTnI, BNP, and CRP to predict the occurrence of MACEs within 12 months after surgery. Sensitive and effective clinical predictive models already exist in cardiac surgery, and biologic variables were dichotomized to allow us to identify only the higher risk stratum of the population. We have arbitrary chosen that patients with biologic markers over the thresholds will present a MACE within 12 months after surgery in 75% of the cases (specificity = 0.75).

To evaluate the improvement of predictive abilities given by the cardiac biomarkers, we performed a multiple backward stepwise logistic regression to assess variables associated with the main endpoint (MACE within 12 months after surgery). We used a semiparsimonious approach. Peak values of cTnI, BNP, and CRP were entered as dichotomous variables using cutoffs obtained with ROC curve analysis. The odds ratios and their 95% confidence interval of variables selected by the logistic model were calculated. The discrimination of the model was assessed using the calculation of the area under the ROC curve (or c statistics). Calibration of the model was assessed using the Hosmer–Lemeshow statistic ($P > 0.05$ for no significant difference between the predictive model and the observed data).[18] Furthermore, logistic models were internally validated using 10-fold cross-validation because it is considered as the most efficient resampling method.[19] This method randomly assigns the patients to 10 equally sized partitions. Subsequently, 9 partitions were used as a learning set and 1 was used as a testing set. This operation was repeated 10 times until each partition was used as testing set.

To assess the association between postoperative biomarkers and cardiac outcome on a long-term basis, a Cox regression model was constructed with the variables identified in the logistic regression and event-free survival curves, at the mean of the covariates, were computed.

All *P* values were two tailed, and a *P* value of less than 0.05 was considered significant. Statistical analysis was performed using SPSS version 16 software (SPSS Inc., Chicago, IL).

Table 1. Baseline Patient Characteristics

Patient Characteristic	Total Cohort, n = 224	Patients with MACE, n = 48	Patients without MACE, n = 176	*P* Value
Age, yr	70 ± 10	72 ± 10	69 ± 10	0.12
Men	157 (70)	38 (79)	119 (68)	0.15
Women	67 (30)	10 (21)	57 (32)	
Body mass index, kg/m^2	27 ± 5	27 ± 5	27 ± 5	0.79
EuroSCORE	5 [0–12]	7 [0–11]	5 [0–12]	< 0.001
Left ventricular ejection fraction, %	63 ± 12	60 ± 11	63 ± 12	0.04
Hypertension	150 (67)	30 (63)	120 (68)	0.49
Myocardial infarction < 4 wk	6 (3)	3 (6)	3 (2)	0.11
Chronic obstructive pulmonary disease	15 (7)	8 (17)	7 (4)	0.004
Diabetes mellitus	38 (17)	12 (25)	26 (15)	0.12
Stroke	11 (5)	1 (2)	10 (6)	0.46
Serum creatinine, μm	103 ± 72	99 ± 23	105 ± 80	0.65
Chronic treatment administered				
Nitrates	53 (24)	11 (23)	42 (24)	1.0
Calcium blockers	45 (20)	10 (21)	35 (20)	0.84
β Blockers	125 (56)	24 (50)	101 (57)	0.41
Renin–angiotensin system inhibitors	108 (48)	26 (54)	82 (47)	0.41
Diuretics	64 (29)	18 (38)	46 (26)	0.14
Statins	114 (51)	25 (52)	89 (51)	0.87
Surgery				
Coronary surgery	100 (45)	15 (31)	85 (48)	
Valve surgery	89 (40)	21 (44)	68 (39)	0.04
Combined cardiac surgery	35 (16)	12 (25)	23 (13)	
Complete revascularization	126/135	23/27	103/108	0.16
Cardiopulmonary bypass time, min	103 [35–232]	104 [53–232]	102 [35–214]	0.40
Type of cardioplegia				
Anterograde	212 (95)	44 (92)	168 (95)	0.48
Anterograde + retrograde	12 (5)	4 (8)	8 (5)	
Time between cardioplegia, min	24 ± 4	25 ± 3	24 ± 4	0.64

Values are mean ± SD, median [extremes], or number (%). A major adverse cardiac event (MACE) was defined as malignant ventricular arrhythmia, myocardial infarction, cardiac dysfunction, the need for myocardial revascularization, and/or death from cardiac cause (see Materials and Methods). Time between cardioplegia was defined as aortic cross clamping time/number of cardioplegia.

EuroSCORE = European System for Cardiac Operative Risk Evaluation.

Results

Two hundred thirty-eight consecutive adult patients underwent surgery during the study period. Fourteen patients (6%) were excluded because of emergency surgery (n = 7), mitral valvuloplasty (n = 2), and other complex or unusual cardiac surgical procedures (n = 5). The remaining 224 patients fulfilled inclusion criteria. Baseline characteristics for this cohort are shown in table 1.

Ten patients (4%) died in the hospital, and 214 patients (96%) were discharged alive. Complete follow-up over the 12-month period after surgery was available in all patients. One-year survival in the global population was 94%. Forty-eight patients (21%) experienced 60 MACEs over the study period. MACEs occurred during in-hospital stay in 28 patients and after discharge in 20 patients. MACEs were malignant ventricular arrhythmia in 12 cases (all observed during in-hospital stay), myocardial infarction in 11 cases (in-hospital: 9 cases), cardiac dysfunction in 23 cases (in-hospital: 13 cases), coronary artery revascularization in 8 cases (percutaneous angioplasty: 8 cases, all performed after discharge), and cardiac death in 6 cases (in-hospital: 3 cases).

The five blood samples were collected in all patients. Serum cTnI peaked 6 h after surgery, and CRP peaked 24 h after surgery (fig. 1). BNP levels gradually increased during the postoperative period, up to 120 h after surgery (fig. 1). Postoperative peak values of cTnI, BNP, and CRP are indicated in table 2. Postoperative peak values of cTnI and BNP were both accurate in predicting the occurrence of MACEs in the global population, whereas the peak level of CRP was of limited diagnostic value, as shown by their respective areas under the ROC curves (table 3). According to the predefined rule of the 75% of specificity, the optimal cutoffs to predict MACEs in the global population were 3.5 ng/ml for cTnI, 880 pg/ml for BNP, and 180 mg/l for CRP (table 3).

We compared patients with MACEs within 12 months after surgery (n = 48) and those without (n = 176). In the univariate analysis, there were significant differences in the incidence of chronic obstructive pulmonary disease (17% *vs.* 4%; $P = 0.004$), in European System for Cardiac Operative Risk Evaluation (EuroSCORE)[20] (7 [0-11] *vs.* 5 [0–12]; $P < 0.001$), in preoperative left ventricular ejection fraction (60 ± 11% *vs.* 63 ± 12%, $P = 0.04$), in type of surgery (coronary surgery, 31% *vs.* 48%; valve surgery, 44% *vs.* 39%; combined cardiac surgery, 25% *vs.* 13%; $P = 0.04$), in the proportion of patients with a peak cTnI above 3.5 ng/ml (72% *vs.* 49%;

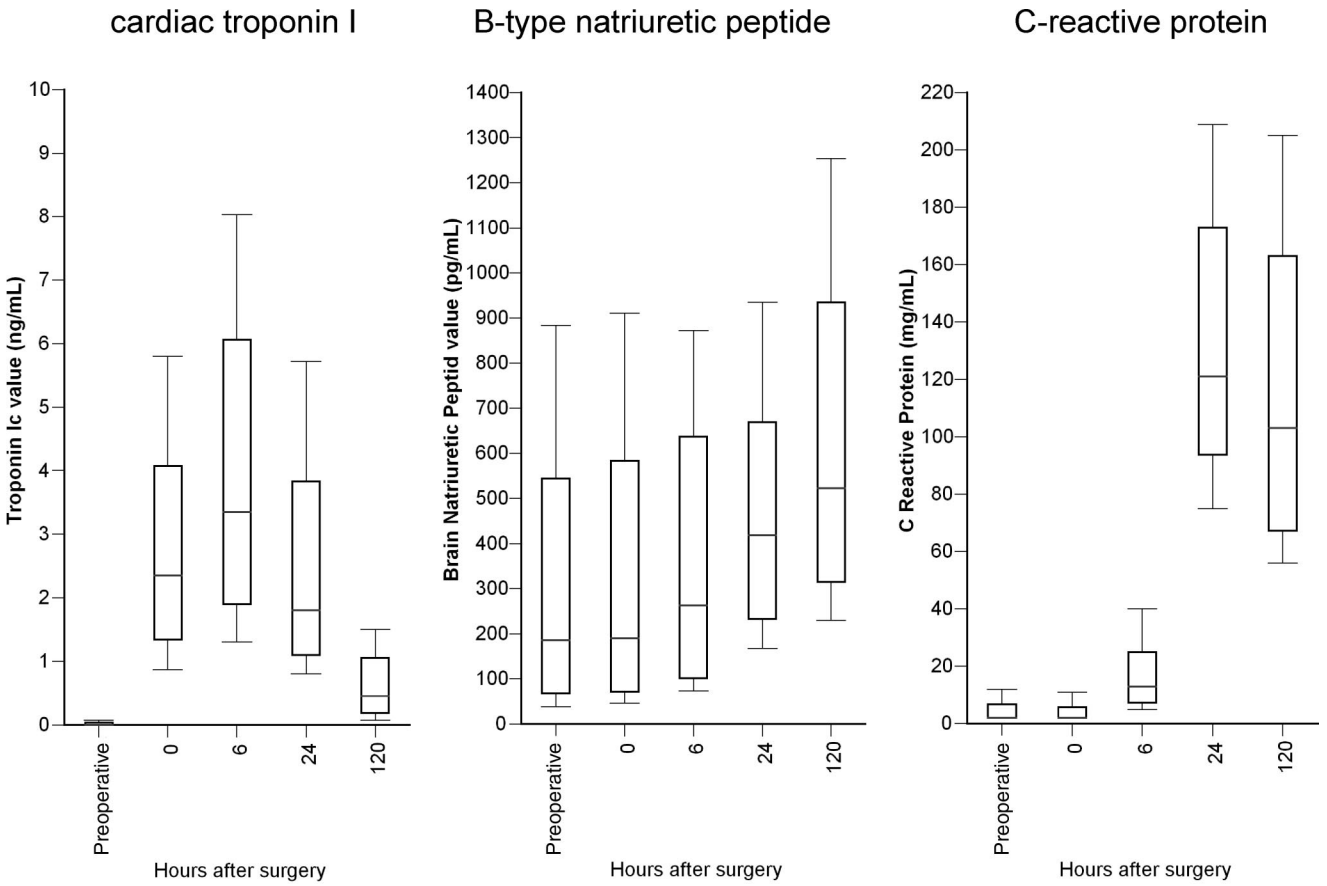

Fig. 1. Time course of postoperative cardiac troponin I, B-type natriuretic peptide, and C-reactive protein release in 224 patients undergoing elective cardiac surgery. For each box plot, *lower* and *upper ends* denote the 25th and 75th percentiles, respectively. The *solid horizontal line* through the box denotes the median of the distribution. The *vertical solid lines* denote the 10th and 90th percentiles.

$P = 0.01$), in the proportion of patients with a peak BNP above 880 pg/ml (46% *vs.* 24%; $P = 0.004$), and in the proportion of patients with a peak CRP above 180 mg/l (40% *vs.* 24%; $P = 0.03$). Using logistic regression, only four variables were significantly and independently associated with MACEs within 12 months after surgery: an elevated cTnI, an elevated BNP, an elevated CRP, and the EuroSCORE (table 4). The model provided good calibration (Hosmer–Lemeshow chi-square test not significant, $P = 0.35$) and discrimination (area under the ROC curve, 0.74 [95% confidence interval, 0.66–0.81]). Discrimination and calibration of the 10-fold cross-validation remained high (0.70 [95% confidence interval, 0.62–0.78] and $P = 0.47$, respectively), meaning that the current model was robust.

Finally, assuming the odds ratios of each cardiac biomarker were close, a Cox model was constructed by including EuroSCORE and the number of elevated cardiac biomarkers. A multiple-biomarker approach including cTnI, BNP, and CRP was more predictive of poor

Table 2. Cardiac Biomarkers

Cardiac Biomarker Peak Value	Total Cohort, n = 224	Patients with MACE, n = 48	Patients without MACE, n = 176	*P* Value
cTnI, ng/ml	3.8 [0.4–70.9]	4.5 [0.8–28.2]	3.4 [0.4–70.9]	0.01
cTnI > 3.5 ng/ml*	120 (54)	34 (72)	86 (49)	0.01
BNP, pg/ml	606 [99–3,953]	852 [141–3,682]	551 [99–3,953]	< 0.001
BNP > 880 pg/ml*	65 (29)	22 (46)	43 (24)	0.004
CRP, mg/l	140 [2–490]	143 [60–490]	140 [2–317]	0.42
CRP > 180 mg/l*	61 (27)	19 (40)	42 (24)	0.03

Values are median [extremes] or number (%). A major adverse cardiac event (MACE) was defined as malignant ventricular arrhythmia, myocardial infarction, cardiac dysfunction, the need for myocardial revascularization, and/or death from cardiac cause (see Materials and Methods).

* Cutoff as defined by receiver operating characteristic curves (table 3).

BNP = B-type natriuretic peptide; CRP = C-reactive protein; cTnI = cardiac troponin I.

Table 3. Analysis of the ROC Curves and Determination of the Thresholds cTnI, BNP, and CRP Predicting the Occurrence of Major Adverse Cardiac Events in 224 Patients Undergoing Cardiac Surgery

	Area Under the ROC Curve [95% CI]	*P* Value	Optimal Cutoff
Peak cTnI, ng/ml	0.62 [0.55–0.68]	0.01	3.5
Peak BNP, pg/ml	0.68 [0.61–0.74]	< 0.001	880
Peak CRP, mg/l	0.54 [0.47–0.60]	0.42	180

BNP = B-type natriuretic peptide; CI = confidence interval; CRP = C-reactive protein; cTnI = cardiac troponin I; ROC = receiver operating characteristic.

outcome than a traditional approach using each biomarker alone (fig. 2).

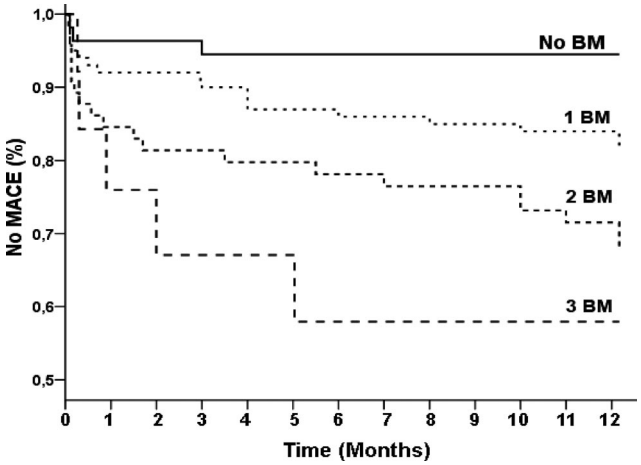

Fig. 2. Cumulative survival at mean of covariates (European System for Cardiac Operative Risk Evaluation) without major adverse cardiac events (MACEs; see definition in the text) according to postoperative elevation of cardiac troponin I (> 3.5 ng/ml), B-type natriuretic peptide (> 880 pg/ml), and C-reactive protein (> 180 mg/l). Patients were categorized according to elevation of no biomarker (BM) (n = 58; survival rate at 1 yr, 95%), only one BM (n = 98; survival rate at 1 yr, 82%), two BMs (n = 56; survival rate at 1 yr, 63%), or three BMs (n = 12; survival rate at 1 yr, 58%). All survival curves significantly differ from each other ($P < 0.05$).

Discussion

The main findings of the current study are that (1) postoperative peak levels of serum cTnI, BNP, and CRP independently predict long-term adverse cardiac outcome following elective cardiac surgery and (2) simultaneous assessment of all three biomarkers to achieve an integrated multiple-marker approach improves the risk assessment of long-term adverse cardiac outcome and provides additional information when compared with a traditional approach using each biomarker alone or EuroSCORE.

Several new cardiac biomarkers have emerged as strong predictors of risk among patients undergoing elective cardiac surgery and are now routinely available to clinicians. Elevated preoperative or postoperative levels of cTnI[3,4,6,21] and BNP[9–11] are associated with higher rates of death and nonfatal cardiac events during the postoperative period. CRP, primarily used as a marker of inflammation, has also been associated with adverse postoperative cardiac outcome after cardiac surgery.[13,14,22,23] The use of a multiple-marker strategy in which patients were categorized based on the number of elevated biomarkers has been validated in the cardiac medical setting.[24] Simultaneous assessment of cTnI, BNP, and CRP enabled powerful prediction of cardiac risk up to 6 months after non–ST-elevation acute coronary syndromes.[24] Moreover, measurements of cTnI in combination with BNP were found to improve risk stratification in advanced heart failure.[25,26] Regarding cardiac surgery, Provenchère *et al.*[12] reported that simultaneous measurement of cTnI and BNP improved the risk assessment of postoperative cardiac dysfunction in 92 consecutive patients undergoing elective cardiac surgery. More recently, high values of both N terminal-proBNP and cTnT measured 24 h after the end of surgery were found to be independently associated with in-hospital cardiac events in elderly patients undergoing elective coronary artery bypass grafting.[27] Our results are in accordance with these findings because we demonstrated in the current study that simultaneous postoperative peak levels of cTnI, BNP, and CRP in combination improved the risk assessment of long-term adverse cardiac outcome after elective cardiac surgery when compared with each biomarker alone. Therefore, the use of a multiple-biomarker strategy, viewed as a whole, could offer complementary information and provide powerful prognostic ability over a broad range of short- and long-term major cardiac events in various types of surgical procedures, allowing clinicians to better stratify postoperative risk in the cardiac surgical setting.

Cardiac troponin I, BNP, and CRP were all independent predictors of long-term adverse cardiac outcome after cardiac surgery in our logistic model. The validation of the model by using 10-fold cross-validation further increases the internal validity of the current results. Well described with postoperative peak value of serum cTnI in previous well-designed studies,[3,5] these results are somewhat different from those recently reported by

Table 4. Predictors of Major Adverse Cardiac Events within 12 Months after Surgery Using Logistic Regression

Variable	Odds Ratio [95% CI]	*P* Value
cTnI > 3.5 ng/ml	2.37 [1.25–5.64]	0.011
BNP > 880 pg/ml	2.65 [1.16–4.85]	0.018
CRP > 180 mg/l	2.14 [1.03–4.49]	0.043
EuroSCORE (per point increase)	1.18 [1.02–1.36]	0.023

Model performances on global population—c statistic: 0.74; Hosmer–Lemeshow statistic: $P = 0.35$. Model performances on cross-validation subsets—c statistic: 0.70; Hosmer–Lemeshow statistic: $P = 0.47$.

BNP = peak value of serum B-type natriuretic peptide; CI = confidence interval; CRP = peak value of serum C-reactive protein; cTnI = peak value of serum cardiac troponin I; EuroSCORE = European System for Cardiac Operative Risk Evaluation.

Provenchère *et al.*,[12] where a single postoperative 24-h measurement of BNP was not an independent predictor of long-term cardiac dysfunction after cardiac surgery in multivariate analysis. Our kinetic study, however, which included several postoperative time points, showed that postoperative BNP concentrations gradually increased up to day 5 after surgery. Consequently, we used a late peak value of BNP, close to discharge BNP concentration, which has been previously found to be more relevant for long-term outcome prediction in the medical setting of acute heart failure.[28]

The areas under the ROC curves we reported in the current study for cTnI, BNP, and CRP measurements ranged from 0.54 to 0.68. These values were lower than those previously reported for cTnI in elective coronary artery bypass surgery.[29] A likely explanation is that both coronary surgery and aortic or mitral valve replacement were included in the present study. Indeed, we recently demonstrated that the diagnostic performance of an elevated cTnI in predicting a severe cardiac event and/or in-hospital death was less in valve surgery than in coronary surgery.[5] Moreover, we described long-term adverse cardiac outcome in the current study rather than in-hospital cardiac morbidity and mortality.

Last, it should be noted that we did not measure postoperative procalcitonin release because the specific assay was unavailable at our institution at the time of the study. Procalcitonin, which recently has been found to be more accurate than CRP for the diagnosis of postoperative infection after cardiac surgery,[30] could be of greater value than CRP for a multiple-biomarker strategy in clinical practice.

Some remarks must be included to indicate the limitations of the current study. First, the study was conducted in a single center. Therefore, the threshold values we reported for each biomarker must be interpreted with caution. Although we used a very efficient method (10-fold cross-validation) to internally validate our model,[19] an external validation using other cohorts provided by other centers is mandatory. For example, because no consensus has been yet reached regarding the optimal anesthetic technique in cardiac surgery, we did not use halogenated anesthetic agents that promote preconditioning[31] in some but not all patients.[32–34] Second, our study does not test appropriate strategies to improve long-term outcome in identified high-risk patients. Future studies should prospectively address this important issue and compare multiple-biomarker strategies with existing cardiac risk scores and clinical predictive models before cardiac biomarkers can be widely recommended for routine clinical practice. Indeed, an increase in cardiac biomarkers may indicate postoperative complications or inappropriate perioperative management (myocardial protection, surgical procedure, sepsis) but also a more severe preexisting disease that could evolve unfavorably on a long-term basis. These two hypotheses are not exclusive but imply different strategies.[6] Last, we assessed the role of postoperative simultaneous elevation of multiple biomarkers on long-term cardiac outcome in the current study. Although 48 patients experienced MACEs, only 20 were out of the hospital. However, regarding statistical power, we considered that it was not appropriate to separate it out. Preoperative values of all these biomarkers could also provide some interesting information, at least for immediate postoperative outcome. This hypothesis was not tested here, and because most of preoperative biomarkers values are within the normal range, a greater sample size should probably be required.

In conclusion, simultaneous measurement of postoperative peak levels of cTnI, BNP, and CRP in combination improves the risk assessment of cardiac adverse outcome within 12 months after elective cardiac surgery with CPB when compared with each biomarker alone. Therefore, the use of different cardiac biomarkers assessing different pathophysiologic mechanisms could provide powerful prognostic ability over a broad range of long-term major cardiac events in various types of cardiac surgical procedures.

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