Preoperative assessment of cardiovascular risk in patients undergoing noncardiac surgery: the Orion study

Giampaolo Scorcu¹, Annarita Pilleri¹, Paolo Contu², Pompilio Faggiano³, Roberto Floris⁴, Alessandra Mereu², Luisella Pistis¹, Roberto Sessegò⁵, Luigi Valentino⁶, Claudia Sardu²

¹Simple Departmental Structure (SSD) of Outpatient Cardiology Consultancy and Evaluation, “G. Brotzu” Hospital, Cagliari; ²Department of Public Health, Clinical and Molecular Medicine, University of Cagliari; ³Cardiology Unit, Spedali Civili, Brescia; ⁴Clinical Cardiology, “San Giovanni di Dio” Hospital, Cagliari; ⁵Departmental Structure of Anesthesia and Analgesic Therapy, “G. Brotzu” Hospital, Cagliari; ⁶Departmental Structure of Cardiology, “G. Brotzu” Hospital, Cagliari, Italy

Abstract

In patients undergoing noncardiac surgery risk indices can estimate patients’ perioperative risk of major cardiovascular complications. The indexes currently in use were derived from observational studies that are now outdated with respect to the current clinical context. We undertook a prospective, observational, cohort study to derive, validate, and compare a new risk index with established risk indices. We evaluated 7335 patients (mean age 63±13 years) who underwent noncardiac surgery. Based on prospective data analysis of 4600 patients (derivation cohort) we developed an Updated Cardiac Risk Score (UCRS), and validated the risk score on 2735 patients (validation cohort). Four variables (i.e. the UCRS) were significantly associated with the risk of a major perioperative cardiovascular events: high-risk surgery, preoperative estimate glomerular filtration rate <30 ml/min/1.73 m², age ≥75 years, and history of heart failure. Based on the UCRS we created risk classes 1, 2, 3 and 4 and their corresponding 30-day risk of a major cardiovascular complication was 0.8% (95% confidence interval [CI] 0.5-1.7), 2.5 (95% CI 1.6-5.6), 8.7 (95% CI 5.2-18.9) and 27.2 (95% CI 11.8-50.3), respectively. No significant differences were found between the derivation and validation cohorts. Receiver operating characteristic (ROC) curves demonstrate a high predictive performance of the new index, with greater power to discriminate between the various classes of risk than the indexes currently used. The high predictive performance and simplicity of the UCRS make it suitable for wide-scale use in preoperative cardiac risk assessment of patients undergoing noncardiac surgery.

Introduction

Preoperative cardiovascular risk estimation is important to facilitate patients making informed decisions about the appropriateness of surgery and to identify at-risk patients who may benefit from enhanced monitoring after noncardiac surgery [1]. Cultural shifts towards advanced care for the elderly along with improvements in surgical techniques and anesthetic techniques have resulted in a substantial increase in the number of older patients with multiple comorbidities undergoing non-cardiac surgery [2]. This evolution has produced a new high-risk patient group that is associated with a high incidence of cardiac death (1-1.5%) and major cardiac complications (2-3.5%) after non-cardiac surgery [3,4].

To stratify patients at risk of perioperative complications, the international guidelines [5-7] recommend using two indexes that are prognostically complementary: the Revised Cardiac Risk Index (RCRI) of Lee et al. [8], and the National Surgical Quality Improvement Program (NSQIP)’s Myocardial Infarction and Cardiac Arrest (MICA) risk calculator [9]. These indexes were, however, derived from patient populations that are now outdated with respect to the current clinical context (RCRI) or were difficult to obtain, needing an on-line risk calculator (MICA).
Therefore, the first index they may lack precision, the other they may not be easy to use in stratifying the risk of the surgical procedure [9-11].

The present study aimed to develop a new, simple and accurate, risk calculator for predicting perioperative cardiovascular complications, based on data that are easy to measure and interpret, to help guide patient decision making and anesthetic and surgical plans in patients referred to noncardiac surgery [12].

Materials and Methods

Study design

The preOperative assessment of cardiovascular RIsk in patients undergoing NOncardiac surgery (ORION) was an observational prospective cohort study. Clinical data were prospectively gathered through an electronic Case Report Form. The study did not involve any drug experimentation, or the use of diagnostic examinations or therapies different from evidence-based guideline recommendations [5-7] or routine clinical practice. The study was approved by the institutional Ethical Committee and written informed consent was obtained from all participants.

Study population

We included all consecutive patients aged 40 years or greater who were admitted for elective or urgent surgery between March 1, 2013 and February 28, 2015 to the “G. Brotzu” Hospital in Cagliari, Italy. Exclusion criteria were: refusal to provide consent and emergency surgery.

Data collection

All patients underwent preoperative clinical assessment including medical history and objective examination with particular focus on the cardiovascular system. Coronary artery disease (CAD) was defined as the presence in the clinical history of any documented event of acute coronary syndrome, positive cardiac stress test, or percutaneous or surgical coronary revascularization. Heart Failure was defined as a documented episode of congestive heart failure, acute pulmonary edema, or paroxysmal nocturnal dyspnea apart from at the time of surgery or the preoperative echocardiographic finding of left ventricular dysfunction in New York Heart Association functional class I-II patients. We estimate preoperative glomerular filtration rate (eGFR) using with the Cockcroft and Gault formula [13]. Body mass index (BMI) was assessed according to the international classification of the World Health Organization [14]. History of transitory ischemic attack (TIA) or stroke was defined by any documented event of transitory (<24 h) or persistent focal loss of neurological functions.

The type of surgery performed, laboratory examinations, cardiac therapy and the appearance of perioperative complications were recorded by authors and coworkers (skilled nurses, anesthetists, cardiologists). In each patient, the surgical, bleeding and, thrombotic risk was calculated [15]. Surgical risk was classified, at the time of the data analysis, based on the European Society of Cardiology/European Society of Anesthesiology (ESC/ESA) classification into three levels: low (incidence of complications <1%), intermediate (1-5%) or high (>5%) [5]. In accordance with current guideline [6] procedure was defined elective when it could be delayed for up to 1 year; urgent when life or limb is threatened if not in the operating room, typically between 6 and 24 h; emergency when life or limb is threatened if not in the operating room, where there is time for no or very limited or minimal clinical evaluation, typically within <6 h. A phone-call follow-up at 30 days from discharge was performed in all patients to evaluate all-cause mortality.

Classification of complications

The primary endpoint consisted of the combination of major perioperative cardiovascular complications within 30 day after surgery: death due to cardiovascular causes, cardiac arrest, acute myocardial infarction (AMI), acute heart failure (HF), Type 2 second-degree atrioventricular block or complete atrioventricular block requiring cardiac pacing, and stroke. Death due to cardiovascular causes was defined as any death for which there was not clearly documented a known or plausible nonvascular cause. Cardiac arrest was defined as the absence of heartbeat or the presence of any arrhythmias (i.e., all forms of malignant ventricular arrhythmia, electromechanical dissociation and asystole) producing a loss of consciousness that required basic or advanced life support. The diagnosis of AMI was confirmed according to the Universal Definition published in 2012 [16]. Monitoring of appearance of AMI were achieved by ECG, by systematically preoperative measurement of biomarker (CK MB only) and if necessary after, and by clinical surveillance. No specific protocol is at our institution. The diagnosis of pulmonary edema required confirmation by chest x-ray and intravenous treatment with diuretics or vasodilators. The diagnosis of stroke was made by an independent neurologist in the presence of focal loss of neurological functions secondary to an ischemic or hemorrhagic event, with residual signs and symptoms lasting for at least 24 h [17], and was confirmed by neuroimaging. All events were adjudicated by study steering committee.

Statistical analysis

Descriptive analyses where performed, according to data distribution, through the calculation of means, medians, percentiles, and percentages. The development of the UCRS was carried out on a cohort of 4600 patients observed between March 1 2013 and May 31 2014 (derivation cohort). First, multivariate logistic regression analysis was performed to identify risk factors associated to major cardiovascular complications, evaluating potential confounding and interaction effects. In the logistic model major cardiac complications was the dependent variable. The following factors were considered as independent variables including type of surgery (high-risk versus medium/low), sex (female versus male), age (>75 versus ≤75 years), BMI class (<18.5; 18.5-<25; ≥25-<30; ≥30), preoperative eGFR <30 ml/min/1.73m², preoperative serum creatinine (>2.0 versus ≤2.0 mg/dl) and the presence or absence of each of the following factors: history of coronary artery disease, congestive HF, stroke or TIA, insulin therapy for diabetes.

The dependent variable was analyzed as a function of the independent variables through a multivariate logistic regression. Starting from a saturated model including all independent vari-
ables, non-significant associated variables (p≥0.05) were consecu-
tively eliminated by mean of a step by step procedure, managed by
researchers. Additionally, the goodness of fit of the models
obtained in each step was assessed through the likelihood statistics.
The association of each independent variable with dependent vari-
able was expressed by means of Odds Ratio (OR) and its 95% con-
fidence interval. The probability of major cardiovascular compli-
cations was calculated based on the final logistic model of estimat-
ed parameters, assessing all possible combinations of identified
risk factors.

Because of the overlapping value of the OR among the vari-
ables, and the consequent similarity of theirs weights, an
unweighted score was created. The resulting UCRS was based
on the ratio between the probability of cardiovascular complica-
tions for each combination of risk factors and that for no risk
factors, obtaining a scale of proportional risk estimates. A score
of 1 was attributed to patients without any of identified risk fac-
tors, a score 2 was attributed to patients with one risk factor and
so on.

To validate the UCRS, logistic regression was repeated in a
second independent cohort of 2735 patients observed between
June 1 2014 and February 28 2015 (validation cohort). In addi-
tion, major cardiovascular complication rates were compared
between the derivation and validation cohorts, and within each
cohort, through Fisher’s chi-square test. Finally, discrimination
was assessed through evaluation of the ROC curves were for the
UCRS and the RCRI, in both the derivation and the validation
cohorts.

Results

Patients’ clinical and demographic characteristics are report-
ed in Table 1. Both sexes were similarly represented and more
than one-quarter of the total study population was aged over 65
years. The derivation and validation cohorts were similar (Table
1) except for a slightly higher prevalence of elective surgery in
the validation cohort, as well as a higher prevalence of interme-
diate-risk noncardiac surgery, GFR <30 ml/min/1.73m², cancer
dyslipidemia. The type of surgery performed is reported in
Table 2. A total of 6,689 patients underwent an elective procedure
(91.2%) and 646 (8.8%) urgent procedure. The number of
low-risk interventions was 4318 (58.9%), while 2495 (34%)

Table 1. Demographic and clinical characteristics of the study patients.

|                                | Total population | Derivation cohort | Validation cohort | p   |
|--------------------------------|------------------|-------------------|------------------|-----|
| Patients, n (%)                | 7335             | 4600 (62.7)       | 2735 (37.3)      | 0.8 |
| Males, n (%)                   | 3844 (52.4)      | 2416 (52.5)       | 1428 (52.2)      |     |
| Age, years, mean ± SD          | 63 ± 13          | 63 ± 13           | 63 ± 13          |     |
| Age ≥75 years, n (%)           | 1596 (21.8)      | 977 (21.2)        | 619 (22.6)       | 0.2 |
| Age 65-74 years, n (%)         | 1913 (26.1)      | 1211 (26.3)       | 702 (25.7)       | 0.5 |
| Elective procedure, n (%)      | 6689 (91.2)      | 4165 (90.5)       | 2524 (92.3)      | 0.01|
| Urgent procedure, n (%)        | 646 (8.8)        | 435 (9.5)         | 211 (7.7)        | 0.01|
| Low-risk surgery, n (%)        | 4318 (58.9)      | 2747 (59.7)       | 1571 (57.4)      | 0.05|
| Intermediate-risk surgery, n (%)| 2405 (34.0)    | 1525 (33.2)       | 970 (35.5)       | 0.04|
| High-risk surgery, n (%)       | 522 (7.1)        | 328 (7.1)         | 194 (7.1)        | 0.9 |
| History of coronary artery disease, n (%) | 604 (8.2) | 372 (8.1)         | 232 (8.5)        | 0.5 |
| History of stroke or TIA, n (%) | 376 (5.1)      | 228 (4.9)         | 148 (5.4)        | 0.4 |
| History of heart failure, n (%) | 255 (3.5)       | 163 (3.5)         | 92 (3.4)         | 0.7 |
| Diabetes insulin-dependent, n (%) | 337 (4.6)      | 214 (4.6)         | 123 (4.5)        | 0.7 |
| CKD - Creatinine >2 mg/dl, n (%) | 330 (4.5)       | 188 (4.1)         | 142 (5.2)        | 0.02|
| CKD - eGFR <30 ml/min/1.73m², n (%) | 352 (4.8)      | 194 (4.2)         | 158 (5.8)        | 0.002|
| Pacemaker/AICD, n (%)          | 146 (2.0)        | 97 (2.1)          | 49 (1.8)         | 0.3 |
| Arterial hypertension, n (%)   | 3144 (42.9)      | 1964 (42.7)       | 1180 (43.1)      | 0.7 |
| Permanent atrial fibrillation, n (%) | 285 (3.9)      | 175 (3.8)         | 110 (4.0)        | 0.6 |
| History of previous cancer, n (%) | 498 (6.8)    | 286 (6.2)         | 212 (7.7)        | 0.01|
| COPD, n (%)                    | 412 (5.6)        | 252 (5.5)         | 160 (5.8)        | 0.5 |
| Vascular disease, n (%)        | 462 (6.3)        | 276 (6.0)         | 186 (6.8)        | 0.2 |
| Hypercholesterolemia, n (%)    | 1609 (21.9)      | 950 (20.6)        | 659 (24.1)       | 0.0006|
| Low MET, n (%)                 | 1156 (15.8)      | 753 (16.4)        | 403 (14.7)       | 0.06|
| BMI normal weight, n (%)       | 3197 (43.6)      | 2017 (43.9)       | 1180 (43.2)      | 0.5 |
| BMI underweight, n (%)         | 145 (2.0)        | 89 (1.9)          | 56 (2.0)         | 0.7 |
| BMI overweight, n (%)          | 3993 (54.4)      | 2494 (54.2)       | 1499 (54.8)      | 0.6 |

TIA, transient ischemic attack; CKD, chronic kidney disease; eGFR, estimate glomerular filtrate rate; AICD, automated implantable cardioverter-defibrillator; COPD, chronic obstructive pulmonary disease; MET, metabolic equivalent; BMI, body mass index.
interventions were intermediate-risk and 522 (7.1%) high-risk. The primary endpoint occurred in 127 patients (1.7%), with 39 cardiac deaths (0.5%). Overall, there were 16 cases of AMI, 81 of acute HF, 19 of cardiac arrest, 2 of advanced AV block and 9 of stroke. Events did not differ significantly between the two cohorts (Table 3).

**Development of the updated cardiac risk score**

The independent variables insulin therapy for diabetes, pre-operative serum creatinine $\geq$2.0 mg/dl, history of stroke or TIA, BMI class, sex, and coronary artery disease did not result significantly ($p<0.05$) associated with the risk of major cardiovascular complications, and consequently were eliminated from the model. The final model identified four variables: high-risk surgery [odds ratio (OR) 5.39; 95% CI 3.29-8.82 $p<0.0001$], history of congestive HF (OR 4.32; 95%CI 2.37-7.85; $p<0.0001$), GFR $<30$ ml/min/1.73m$^2$ (OR 3.11; 95%CI 1.67-5.79; $p<0.0001$) and age $\geq$75 years (OR 2.67; 95%CI 1.69-4.23; $p<0.0001$) as significantly associated with the risk of major cardiovascular complications (Table 4).

We identified four classes of risk according to the different combinations of risk factors and relative probability of cardiovascular complications (updated cardiac risk score). Class 1 (probability of major cardiovascular complications: 0.8%; 95% CI 0.5-1.7) signifying none of the identified risk factors present. Class 2 (probability of complications: 2.5%; 95% CI 1.6-5.6) signifying only one factor present. Class 3 (probability of complications: 8.7%;

| Table 2. Type of surgery. | Patients, n (%) |
|--------------------------|-----------------|
| Kidney, liver, pancreas transplant | 81 (1.1) |
| Minor urology            | 966 (13.2) |
| Major urology            | 309 (42) |
| Minor gynecology/obstetrics | 907 (12.4) |
| Major gynecology/obstetrics | 128 (1.7) |
| Abdominal                | 942 (12.8) |
| Anorectal                | 189 (2.6) |
| Hernia inguinal/umbilical/epigastric, splanchnocele | 399 (5.4) |
| Minor orthopedics        | 565 (7.7) |
| Major orthopedics        | 177 (2.4) |
| Neurosurgery             | 574 (7.8) |
| Vertebral column         | 215 (2.9) |
| Vascular                 | 636 (8.7) |
| Thoracic                 | 81 (1.1) |
| Breast                   | 382 (5.2) |
| Gastrointestinal endoscopy | 263 (3.6) |
| Plastic/reconstruction   | 247 (3.4) |
| Ear-nose-throat          | 181 (2.5) |
| Maxillofacial            | 70 (1.0) |
| Eye                      | 23 (0.3) |

| Table 3. Major cardiac complications in the derivation and validation cohorts. | |
|--------------------------|--------------------------|--------------------------|
|                         | Derivation cohort (n=4600) | Validation cohort (n=2735) | p |
| Total major cardiac complications, n (%) | 82 (1.8) | 45 (1.6) | 0.6 |
| Myocardial infarction | 12 (0.3) | 4 (0.1) | 0.3 |
| Acute pulmonary edema | 53 (1.2) | 28 (1.0) | 0.6 |
| Cardiac arrest         | 11 (0.2) | 8 (0.3) | 0.7 |
| Total atrioventricular block | 2 (0.04) | 0 | 0.3 |
| Stroke                  | 4 (0.09) | 5 (0.2) | 0.2 |
| Cardiac mortality       | 23 (0.5) | 16 (0.6) | 0.6 |
| Noncardiac mortality    | 59 (1.3%) | 17 (0.6 %) | 0.007 |
| All-cause mortality     | 82 (1.8 %) | 33 (1.2 %) | 0.05 |

| Table 4. Multivariate logistic regression analysis in the derivation cohort: factors significantly associated (p<0.05) to a risk of major cardiovascular complications. | |
|--------------------------|--------------------------|--------------------------|--------------------------|
| Risk factors             | Odds ratio | 95% Confidence interval | p |
| Derivation cohort        |             |                         |                              |
| High-risk surgery        | 5.39       | 3.29                    | 8.82                       | <0.0001 |
| Heart failure            | 4.32       | 2.37                    | 7.85                       | <0.0001 |
| eGFR <30 ml/min/1.73m$^2$ | 3.11       | 1.67                    | 5.79                       | <0.0001 |
| Age ≥75 years            | 2.67       | 1.69                    | 4.23                       | <0.0001 |
| Validation cohort        |             |                         |                              |
| High-risk surgery        | 3.46       | 1.67                    | 7.17                       | 0.001 |
| Heart failure            | 7.45       | 3.47                    | 15.99                      | <0.0001 |
| eGFR <30 ml/min/1.73m$^2$ | 4.84       | 2.39                    | 9.79                       | <0.0001 |
| Age ≥75 years            | 4.60       | 2.34                    | 9.08                       | <0.0001 |
95% CI 5.2-18.9) signifying two factors present. Class 4 (probability of complications: 27.2%; 95% CI 11.8-50.3) signifying three or more factors present (Table 5).

### Validation of the updated cardiac risk score

Multivariate logistic regression analysis on the validation cohort gave similar results to those obtained on the derivation cohort, identifying the same independent variables in association to major cardiovascular complications: high-risk surgery (OR 3.46; C.I. 95% 1.67-7.17; p=0.001), history of congestive HF (7.45; 95%CI 3.47-15.99; p=0.0001), GFR <30/ml/min/1.73m² (8.44; 95% CI 2.39-9.79; p=0.0001), and age ≥75 years (4.60; 95%CI 2.34-9.08; p<0.0001).

The derivation and validation cohorts did not show significant differences concerning the frequency of major cardiovascular complications when stratified for risk class by either the UCRS or RCRI. In each of the two cohort, the frequency of complications between classes 1 and 2 identified by UCRS resulted significantly higher in class 2; likewise between classes 2 and 3 resulted significantly higher in class 3 and between classes 3 and 4 resulted significantly higher in class 4. Conversely, in the same cohorts when stratified by RCRI, the risk of complications increases across all 4 risk classes, but the higher frequency of complications stratified by risk class reaches statistical significance only for class 2 compared to class 1 (Table 6).

ROC curves for the derivation cohort (Figure 1) showed a greater area under the curve for the UCRS than RCRI (0.77±0.03 versus 0.72±0.03, respectively). Similarly, the validation cohort (Figure 2) showed a greater area under the curve for the UCRS than RCRI (0.86±0.03 versus 0.79±0.04).

### Table 5. Updated cardiac risk score.

| Risk classes | Risk factor | Mean probability of major cardiovascular complications | 95% Confidence interval |
|--------------|-------------|--------------------------------------------------------|-------------------------|
| 1            | None        | 0.8%                                                   | 0.5%                    | 1.7%                    |
| 2            | One risk factor | 2.5%                                           | 1.6%                    | 5.6%                    |
| 3            | Two risk factors | 8.7%                                              | 5.2%                    | 18.9%                   |
| 4            | Three risk factors | 27.2%                                            | 11.8%                   | 50.3                    |

### Table 6. Frequency of major cardiovascular complications stratified by risk class and cohort.

|                    | Derivation cohort | Validation cohort |
|--------------------|-------------------|-------------------|
|                    | Population | Events | Rate | Population | Events | Rate |
| **Updated cardiac risk score** |          |         |      |            |         |      |
| Class I            | 3243       | 20      | 0.6% | 1887       | 4       | 0.2% |
| Class II           | 1079       | 33      | 3.1% | 664        | 17      | 2.6% |
| Class III          | 246        | 24      | 9.8% | 155        | 16      | 10.3%|
| Class IV           | 32         | 5       | 15.6%| 29         | 6       | 20.7%|
| **RCRI**           |            |         |      |            |         |      |
| Class I            | 3495       | 29      | 0.8% | 2044       | 9       | 0.4% |
| Class II           | 809        | 31      | 3.8% | 492        | 20      | 4.1% |
| Class III          | 218        | 13      | 6.0% | 168        | 9       | 5.4% |
| Class IV           | 78         | 9       | 11.5%| 31         | 5       | 16.1%|

Figure 1. Derivation cohort: ROC curves comparing the sensitivity and specificity between the updated cardiac risk and the RCRI.
Discussion

The main finding of our study was the identification of four independent variables that were significantly associated to perioperative cardiovascular events both in the derivation and validation cohorts: high-risk surgery, history of HF, GFR < 30 ml/min/1.73m², and age ≥75 years. The presence of one or more of these variables permits, by means of a UCRS, to classify candidates for noncardiac surgery into four different classes of risk with a progressively greater probability of perioperative cardiovascular complications.

The need to elaborate a new algorithm for risk stratification is due to intrinsic limitations [2,11] of the indexes currently recommended by international guidelines: the RCRI [7] and NSQIP-MICA risk calculator [8]. The RCRI was formulated based on patient data gathered between 1989 and 1994 (i.e. more than twenty years ago), and it is now outdated. The NSQIP-MICA model, though more recent, employs a very complex algorithm that mandatory requires the use of a computer. Our UCRS instead, is easy to remember by physician, quick to use even bedside, and provides a satisfactory and accurate risk estimation. Otherwise, also MICA perform a risk estimation that may be sometimes inaccurate by subjective interpretation of some of its variables (ASA classification [18,19] or preoperative functional status).

Among the variables identified in our study, surgery type is a factor common to the previous indexes, but our risk estimation, in line with the latest guidelines classification [5,6], defines it in terms of the specific organ involved, not just the anatomical region (vascular, chest or abdominal surgery) as in the RCRI [7,10]. Our patient population refers to the contemporary context of surgery candidates, and patients were enrolled consecutively without selection apart from the minimum age and non-emergency procedure requirement. Hence, also patients submitted to low-risk surgery were enrolled hypothesizing that, if other predictive variables were present, the risk of complications would not be negligible. In contrast to the previous indexes, we evaluated renal function by eGFR which, compared to creatininemia alone, is more reliable, sensitive and specific [19]. History of HF is a common variable to the RCRI and other studies [20,21] but not to the NSQIP. This factor in our study showed a strong association with risk of complications. Age was a common factor to the NSQIP but its role there is rather controversial: ESC/ESA guidelines [5] do not attribute to it an independent role in increasing the risk of complications but rather link it to the greater incidence of comorbidities in the elderly; on the contrary, the ACC/AHA guidelines [6] assign a key role to age in predicting complications. Some reports claim that age plays an unfavorable role in noncardiac surgery [22-26] but in the RCRI it is not correlated to complications. Nevertheless, applying RCRI to other patient populations and integrating it with age [4], the area under the ROC curve for prediction of major events increases markedly [10]. In our study, multivariate logistic regression analysis indicated that age ≥75 years was associated to an increased incidence of cardiovascular complications: the incidence increases almost four-fold.

In contrast to the previous indexes, our study did not find that insulin-treated diabetes, creatinine >2 mg/dl, history of stroke or TIA or history of ischemic heart disease were associated to the risk of cardiovascular complications after surgery. The non-significance of diabetes, in line with previous reports in the NSQIP, likely reflects improvements in hypoglycemic agents [24] and a greater attention to disease control in recent years [27]. Similarly, the determination of CKD by means of creatinine is now considered insufficiently reliable, and is not recommended by guidelines [20]. In our study, which enrolled patients with stable CAD, a history of ischemic heart disease, in contrast to the RCRI, was not associated with an increased incidence of complications. This may be explained by the optimization of medical therapy and the refinement of surgical and percutaneous revascularization techniques in recent decades [28]. Prophylactic coronary revascularization before major surgery in patients even with severe CAD did not confer any benefit compared to optimal medical management in terms of perioperative mortality and myocardial infarction in the largest trial in this topic and that in asymptomatic or stable CAD patients were no differences in complications between aggressive and non-aggressive therapy in a metanalysis [29,30].

There are several reports of the problem of detecting perioperative infarction. It is known that the occurrence of perioperative AMI is often asymptomatic; hence, an insufficient accuracy in the definition of infarction and inadequate periprocedural monitoring could lead to the underestimation of this complication in the general population and, on the contrary, a selective overestimation in patients with a positive history of ischemic heart disease [10]. In our study, which involved an accurate, uniform monitoring of perioperative infarction, history of ischemic heart disease was not associated with an increased incidence of perioperative complications.

A significant finding of our study was the development and validation of a UCRS based on the combination of the four variables identified. The UCRS was shown to be highly predictive of complications and, otherwise the RCRI, is capable of stratifying the risk in a contemporary patient population undergoing surgery and has a greater capacity to discriminate between patients at high and low risk, as demonstrated by the significant difference between the different classes in both cohorts. Compared to the NSQIP-MICA risk calculator the UCRS is practical and easy to use and is not limited to predicting the probability of myocardial infarction and cardiac arrest but evaluates a wider range of complications, without though relying on variables defined and condi-
tioned by subjective interpretation such as the classification of risk according to the American Society of Anesthesiology [31] or the description of functional status.

Study limitations

Our study, monocentric and observational, may contain some data collection bias. The risk of a bias of information was minimized by the mode of data collection; the prospective analysis of patients admitted consecutively to our department, the use of variables of a highly objective nature and of hard endpoints such as all-cause mortality at 30 days limited such risk. The estimate of risk nevertheless cannot be generalized to all patient subgroups in that we excluded cardiac patients, of whatever origin, who were not in a clinically stable condition. It should nevertheless be pointed out that such patients constitute only a small part of all non-selected patients. On the other hand, the selection criteria adopted enabled us to enroll the majority of patients, representative of those today undergoing noncardiac surgery in a nonemergency situation, thus rendering the score widely generalizable. In our study the patients were systematically monitored after surgery with CKMB and not with troponin, although this is the preferred marker by Universal Definition of AMI [16]. Nevertheless however, CK MB is a reliable marker of Myocardial Infarction and the clinical significance of myocardial injury after noncardiac surgery (MINS) measured by troponins is yet a matter to debate [32]. We acknowledge that patients were not systematically followed in the hospital by a member of the study team to ensure no cardiovascular complications were missed. However, our surveillance employs routine protocol at our institution, based on skilled nurse attendance and physician supervision.

Conclusions

In this study, we have developed a simple risk score for predicting major cardiac complications in patients undergoing noncardiac surgery, which outperformed the RCRI. Our data, gathered from a patient population that was ethnically relatively homogeneous, may be likely generalizable and it is hoped that this risk score will be investigated also in other patient populations. In particular, further research is needed to validate the UCRS in multicenter independent populations. We believe that this instrument will favor a better coordination and integration among the diverse health professionals involved in preoperative assessment, so improving patients’ clinical management.

References

1. Rose J, Weiser TG, Hider P, et al. Estimated need for surgery worldwide based on prevalence of diseases: a modelling strategy for the WHO Global Health Estimate. Lancet Glob Health 2015;3:S13-20.
2. Carmo G, Calderaro D, Yu PC, et al. Perioperative cardiovascular evaluation: heads or tails? Rev Assoc Med Bras 2012;58:505-12.
3. Haynes AB, Weiser TG, Berry WR, et al. Safe Surgery Saves Lives Study Group. A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med 2009;360:491-9.
4. Devereaux PJ, Chan MT, Alonso-Coello P, et al. Association between post-operative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012;307:2295-304.
5. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on noncardiac surgery: cardiovascular assessment and management. The Joint Task Force on noncardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J 2014;35:2383-431.
6. Fleisher LA, Fleischmann KE, Auerbach AD, et al. ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. J Am Coll Cardiol 2014;64:e77-137.
7. Ducette E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. J Am Coll Cardiol 2017;63:17-32.
8. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043-9.
9. Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation 2011;124:381-7.
10. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the LEE cardiac risk index. Am J Med 2005;118:1334-41.
11. Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. Ann Intern Med 2010;152:26-35.
12. Katz RI, Cimino L, Vitkun SA. Preoperative medical consultations: impact on perioperative management and surgical. Can J Anesth 2005;52:7-697.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
14. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. WHO Technical Report Series 854; Geneva; 1995.
15. Rossini R, Musumeci G, Visconti LO, et al. Perioperative management of antplatelet therapy in patients with coronary stents undergoing cardiac and noncardiac surgery: a consensus document from Italian cardiological, surgical and anesthesiologica societies. EuroIntervention 2014;10:38-46.
16. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67.
17. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century. A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:2064-89.
18. Aronson WL, McAuliffe MS, Miller K. Variability in the American Society of Anesthesiologists Physical Status Classification Scale. AANA J 2003; 1:265-74.
19. Mak PH, Campbell RC, Irwin MG. The ASA physical status classification: inter-observer consistency. Anaesth Intensive Care 2002;30:633-40.
20. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1-150.
21. Upshaw J, Kiernan MS. Pre-operative cardiac risk assessment for noncardiac surgery in patients with heart failure. Curr Heart Fail Rep 2013;10:147-56.
22. Hammill BG, Curtis LH, Bennet-Guerrero E, et al. Impact of heart failure on patients undergoing major noncardiac surgery. Anesthesiology 2008;108:559-67.
23. Naughton C, Feneck RO. The impact of age on 6-month survival in patients with cardiovascular risk factors undergoing elective noncardiac surgery. Int J Clin Pract 2007;61:768-76.
24. Donati A, Ruzzi M, Adrario E, et al. A new and feasible model for predicting operative risk. Br J Anaesth 2004;93:393-9.
25. Priebe HJ. The aged cardiovascular risk patient. Br J Anaesth 2000;85:763-78.
26. Andersson C, Wissenberg M, Jørgensen ME, et al. Age-specific performance of the revised cardiac risk index for predicting cardiovascular risk in elective noncardiac surgery. Circ Cardiovasc Qual Outcomes 2015;8:103-8.
27. American Diabetes Association. Strategies for improving care. Diabetes Care 2016; 39:S6-S12.
28. Roger VL, Go AS, Lloyd-Jones DM, et al. On behalf of the American Heart Association Statistic Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics - 2012 update: a report from the American Heart Association. Circulation 2012; 125:e2-220.
29. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 2004;351:2795-804.
30. Wong EY, Lawrence HP, Wong DT. The effects of prophylactic coronary revascularization or medical management on patient outcomes after noncardiac surgery: a meta-analysis. Can J Anaesth 2007;54:705-17.
31. Haynes SR, Lawler PG. An assessment of the consistency of ASA physical status classification allocation. Anaesthesia 1995;50:195-9.
32. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2017;317:1642-51.