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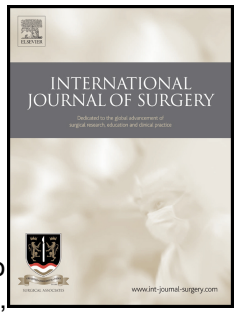

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Francesco Nicolini, Giuseppe Santarpino, Giuseppe Gatti, Daniel Reichart, Francesco Onorati, Giuseppe Faggian, Magnus Dalén, Sorosh Khodabandeh, Theodor Fischlein, Daniele Maselli, Saverio Nardella, Antonino S. Rubino, Marisa De Feo, Antonio Salsano, Riccardo Gherli, Giovanni Mariscalco, Eeva-Maija Kinnunen, Vito G. Ruggieri, Karl Bounader, Matteo Saccocci, Sidney Chocron, Juhani Airaksinen, Andrea Perrotti, Fausto Biancari

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Utility of Glycated Hemoglobin Screening in Patients Undergoing Elective Coronary Artery Surgery: Prospective, Cohort Study from the E-CABG Registry

Running title: HbA1c in elective CABG

Francesco Nicolini,[a] MD, PhD, Giuseppe Santarpino,[b] MD, PhD, Giuseppe Gatti,[c] MD, Daniel Reichart,[d] MD, Francesco Onorati,[e] MD, PhD, Giuseppe Faggian,[e] MD, PhD, Magnus Dalén,[f] MD, PhD, Sorosh Khodabandeh,[f] MD, Theodor Fischlein,[b] MD, PhD, Daniele Maselli,[g] MD, Saverio Nardella,[g] MD, Antonino S. Rubino,[h] MD, PhD, Marisa De Feo,[i] MD, PhD, Antonio Salsano,[l] MD, Riccardo Gherli,[m] MD, Giovanni Mariscalco,[n] MD, PhD, Eeva-Maija Kinnunen,[o] MD, PhD, Vito G. Ruggieri,[p] MD, PhD, Karl Bounader,[p] MD, Matteo Saccocci,[q] MD, Sidney Chocron,[r] MD, Juhani Airaksinen,[s] MD, PhD, Andrea Perrotti,[r] MD, PhD, and Fausto Biancari,[o,s,t] MD, PhD

[a]Division of Cardiac Surgery, University of Parma, Parma, Italy;
[b]Cardiovascular Center, Paracelsus Medical University, Nuremberg, Germany;
[c]Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy;
[d]Hamburg University Heart Center, Hamburg, Germany;
[e]Division of Cardiovascular Surgery, Verona University Hospital, Verona, Italy;
[f]Department of Molecular Medicine and Surgery, Department of Cardiothoracic Surgery and Anesthesiology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden;
[g]Department of Cardiac Surgery, St. Anna Hospital, Catanzaro, Italy;
[h]Centro Cuore Morgagni, Pedara, Italy;
[i]Division of Cardiac Surgery, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy;
[l]Division of Cardiac Surgery, University of Genoa, Genoa, Italy;
[m]Department of Cardiovascular Sciences, Cardiac Surgery Unit, S. Camillo-Forlanini Hospital, Rome, Italy;
[n]Department of Cardiovascular Sciences, Clinical Sciences Wing, University of Leicester, Glenfield Hospital, Leicester, UK;
[o]Department of Surgery, Oulu University Hospital and University of Oulu, Oulu, Finland;
[p]Division of Cardiothoracic and Vascular Surgery, Pontchaillou University Hospital, Rennes, France;
[q]Department of Cardiac Surgery, Centro Cardiologico–Fondazione Monzino IRCCS, University of Milan, Italy ;
[r]Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France;
[s]Heart Center, Turku University Hospital and University of Turku, Turku, Finland;
[t]Department of Surgery, University of Turku, Turku, Finland.

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Corresponding Author:
Prof. Fausto Biancari,
Heart Center,
Turku University Hospital,
PO Box 52, 20521 Turku
E-mail: faustobiancari@yahoo.it

ABSTRACT

Background: Patients with increased glycated hemoglobin (HbA1c) seem to be at increased risk of sternal wound infection (SWI) after coronary artery bypass grafting (CABG). However, it is unclear whether increased baseline HbA1c levels may affect other postoperative outcomes.

Material and methods: Data on preoperative levels of HbA1c were collected from 2606 patients undergoing elective isolated CABG from 2015 to 2016 and included in the prospective, multicenter E-CABG registry.

Results: The prevalence of HbA1c ≥53 mmol/mol (7.0%) among non-diabetics was 5.3%, among non-insulin dependent diabetics was 53.5% and among insulin dependent diabetics was 67.1% (p<0.001). The prevalence of HbA1c >75 mmol/mol (9.0%) among non-diabetics was 0.5%, among non-insulin dependent diabetics was 5.8% and among insulin dependent diabetics was 10.6% (p<0.001). Baseline levels of HbA1c ≥53 mmol/mol (7.0%) was a significant predictor of any SWI (10.7% vs. 3.3%, adjusted p-value: <0.001), deep SWI/mediastinitis (3.8% vs. 1.3%, adjusted p-value: 0.001) and acute kidney injury (27.4% vs. 19.8%, adjusted p-value: 0.042). These findings were confirmed in multilevel mixed effect logistic regression adjusted for participating centers. Among patients with diabetes, HbA1c ≥53 mmol/mol (7.0%) was predictive of SWI (11.1% vs. 4.8%, p=0.001).

Conclusions: HbA1c is increased in a significant proportion of patients undergoing elective CABG and these patients are at higher risk of SWI. Less clear is the impact of increased HbA1c on other postoperative outcomes. These results do not support screening of HbA1c in patients without history of diabetes. Preoperative screening of HbA1c is valuable only to identify diabetics at risk of SWI.

Abstract word count: 249 words

Key-words: Coronary artery bypass; CABG; diabetes; HbA1c; glycated hemoglobin.

1. Introduction

Diabetics are at increased risk for of surgical site infections, and such a risk seems to be highest in patients undergoing cardiac surgery [1]. Poor glycemic control is known to increase the risk of infections [2]. This susceptibility to infectious diseases is secondary to the formation of advanced glycation end products, which can affect several immune response pathways [3-5]. Hyperglycemia is responsible also for the non-enzymatic irreversible formation of glycated hemoglobin (HbA1c). HbA1c is eliminated at the end of red blood cell lifespan, which is on average 116 days [6], and monitoring this biomarker allows the estimation of blood glucose levels over the previous 3- to 4-month period [7]. Optimization of glycemic control seems to reduce the risk of infection [8]. Increased preoperative levels of HbA1c seems to be associated with a higher risk of sternal wound infection (SWI) in patients undergoing coronary artery bypass grafting (CABG) [9-11]. However, it is not clear whether HbA1c as an indicator of poor glycemic control may predict other early adverse events after cardiac surgery [12]. This issue was investigated in the present study evaluating the outcome of patients undergoing elective, isolated CABG.

2. Methods

This is a prospective, cohort study from the multicenter E-CABG registry which enrolled patients undergoing isolated CABG from 16 European centers of cardiac surgery (Besançon, France; Catanzaro, Italy; Genoa, Italy; Hamburg, Germany; Milan, Italy; Leicester, UK; Nuremberg, Germany; Naples, Italy; Oulu, Finland; Parma, Italy; Pedara, Italy; Rennes, France; Rome, Italy; Stockholm, Sweden; Trieste, Italy; Verona, Italy). A dedicated Access datasheet was employed for data entry. Data was prospectively collected by trained researchers and/or nurses and was further checked at each participating center before submitting dataset to the principal investigator for merging. The principal investigator evaluated the databases for consistency by asking for missing and random data. This study is registered in Clinicaltrials.gov (Identifier: NCT02319083). Its detailed protocol and definition criteria were published elsewhere [13]. The Institutional Review Board of all the participating centers approved this study. This work has been reported in line with the STROCSS criteria [14].

2.1. Eligibility criteria and treatment methods

Out of 7352 consecutive patients operated on from January 2015 to December 2016 and enrolled in the E-CABG registry, 4300 patients had their serum level of HbA1c measured at admittance to the hospital for the index procedure. In order to avoid the confounding effect of acute coronary syndrome and urgent/emergency procedures on the immediate postoperative outcome and because preoperative optimization of glycemic control is feasible only before elective surgery, patients undergoing urgent or emergency procedure were excluded from this analysis. Therefore, 2606 patients fulfilled the inclusion criteria and were included in the present analysis. Patients' characteristics and operative variables of these patients are summarized in Table 1. None of the participating centers adopted a tight postoperative glycemic control, but blood glucose levels were accepted being in a range between 8.0 mmol/L and 11.0 mmol/L during the postoperative period.

2.2. Outcomes

The outcomes of this study were in-hospital death, SWI of any severity, deep SWI/mediastinitis, stroke, acute kidney injury and prolonged inotropic support. SWI, stroke, acute kidney injury and prolonged inotropic support were chosen as main outcomes of this study as these adverse events are most likely to be affected by suboptimal glycemic control and they have an impact on late outcome. The diagnosis and severity of SWI was defined and graded according to the Centers for Disease Control and Prevention classification of the surgical site infections [15]. Stroke was defined as any focal or global neurological syndrome occurring during the in-hospital stay caused by ischemia and/or hemorrhage not resolving within 24 h. The diagnosis and nature of stroke is made on the basis of findings at computed tomography and/or magnetic resonance imaging of the brain and confirmed by a neurologist. Definition criteria of the other end-points are reported in detail elsewhere [13]. The severity of postoperative acute kidney injury was defined according to the KDIGO criteria [16]. Patients with a preoperative estimated glomerular filtration rate <15 mL/min/m^2 or preoperatively on dialysis were excluded from the subanalysis of the occurrence of postoperative acute kidney injury.

Prolonged inotropic support refers to the use of use of epinephrine, norepinephrine, milrinone, amrinone, dobutamine, dopamine, levophed and/or levosimedan for > 12 h after surgery.

2.3. Data analysis

Statistical analysis was performed using the SPSS v. 23.0 statistical software (IBM Corporation; Armonk, New York, USA) and the Stata v. 14.0 statistical software (StataCorp LLC, College Station, Texas, USA). No attempt to replace missing values was made. Continuous variables were reported as the mean and standard deviation. Nominal variables were reported as counts and percentages. Fisher's exact test, Chi-square test, Mann-Whitney test and Spearman test were used for univariate analysis. HbA1c values were reported as mmol/mol according to the International Federation of Clinical Chemistry units as well as percentages according the National Glycohemoglobin Standardization Program (NGSP) units. The prognostic impact of baseline HbA1c was evaluated first as a continuous variable and then as a dichotomized variable according to a cut-off value of 53 mmol/mol (NGSP units, 7.0%) as suggested both for diagnosis and optimal glycemic control of diabetes (10). Further analyses were performed employing a cut-off value of HbA1c of 75 mmol/mol (NGSP units, 9.0%) as this value is an indicator of poor glycemic control [17]. The risk estimate of adverse events was adjusted for the following covariates: age, gender, body mass index, hemoglobin, HbA1c, CKD-EPI estimated glomerular filtration rate, stroke, pulmonary disease, extracardiac arteriopathy, left ventricular ejection fraction ≤50%, recent myocardial infarction, bilateral internal mammary artery grafting and units of transfused red blood cells. Resternotomy for bleeding was included in the regression model evaluation SWIs. In view of possible interinstitutional difference in terms of surgical technique of sternal wound closure and postoperative care, multilevel mixed-effects logistic regression was performed for interinstitutional analysis of the impact of baseline HbA1c on SWI as adjusted for the above mentioned covariates. The predictive ability of the HbA1c to predict binary adverse postoperative events was evaluated using the receiver-operating characteristic curve (ROC) method and evaluating the area under the curve (AUC). Non-parametric regression ROC analyses based on 1000 bootstrap replications were also performed to adjust the serum level of HbA1c for the above

listed covariates. Logistic regression was used to adjust the impact of covariates on binary outcomes. All tests were two-sided with the alpha level set at 0.05 for statistical significance.

3. Results

3.1. Prevalence of increased HbA1c levels

The prevalence of HbA1c ≥53 mmol/mol (NGSP units, 7.0%) among patients with undiagnosed diabetes was 5.3%, among non-insulin dependent diabetics was 53.5% and among insulin dependent diabetics was 67.1% (p<0.001). The prevalence of HbA1c >75 mmol/mol (NGSP units, 9.0%) among patients with undiagnosed diabetes was 0.5%, among non-insulin dependent diabetics was 5.8% and among insulin dependent diabetics was 10.6% (p<0.001).

3.2. Prognostic impact of HbA1c in the overall series

Unadjusted AUC of ROC curves showed that increased baseline levels of HbA1c were associated with higher risk of any SWI, deep SWI/mediastinitis and acute kidney injury (Tab. 2). Adjusted AUC of ROC curves confirmed only the increased risk of any SWI and deep SWI/mediastinitis (Tab. 2). Baseline HbA1c was not associated with any of the other outcomes.

Baseline level of HbA1c included as a continuous variable in to regression models was an independent predictor of any SWIs, deep SWI/mediastinitis and acute kidney injury (Tab. 3).

Multilevel mixed effects logistic regression adjusted for participating centers and the above listed covariates confirmed the impact of baseline HbA1c on the risk of postoperative SWI (per unit of HbA1c, OR 1.035, 95%CI 1.023-1.047), deep SWI/mediastinitis (per unit of HbA1c, OR 1.028, 95%CI 1.009-1.048) and acute kidney injury (per unit of HbA1c, OR 1.018, 95%CI 1.003-1.019).

When HbA1c was dichotomized, a baseline levels of HbA1c ≥53 mmol/mol (NGSP units 7.0%) was a significant predictor of any SWI (crude rates, 10.7% vs. 3.3%, adjusted p-value: <0.001, OR 3.221, 95%CI 2.224-4.665), deep SWI/mediastinitis (crude rates, 3.8% vs. 1.3%, adjusted p-value: 0.001, OR 2.717, 95%CI 1.508-4.895) and acute kidney injury (crude rates, 27.4% vs. 19.8%, adjusted p-value: 0.042, OR 1.468, 95%CI 1.178-1.829).

Multilevel mixed effects logistic regression adjusted for participating centers and the above listed covariates confirmed the impact of baseline HbA1c ≥53 mmol/mol (NGSP units 7.0%) on the risk of postoperative SWI (OR 2.897, 95%CI 1.953-4.297), deep SWI/mediastinitis (OR 2.428, 95%CI 1.293-4.561) and acute kidney injury (OR 1.292, 95%CI 1.017-1.641).

The results of stratified analysis for increasing cutoff values of baseline HbA1c showed that this biomarker was an independent predictor only of any SWI as well as deep SWI/mediastinits (Tab. 4). These findings were confirmed in multilevel mixed effect logistic regression (any SWI: HbA1c 53-75 mm/ml, OR 2.605, 95%CI 1.715-3.956, >75 mmol/mol, OR 4.763, 95%CI 2.469-9.190; deep SWI/mediastinits: HbA1c 53-75 mm/ml, OR 2.131, 95%CI 1.086-4.181, >75 mmol/mol, OR 4.294, 95%CI 1.574-11.712).

3.3. HbA1c and outcome in patients with and without history of diabetes

Among patients without history of diabetes, ROC curve analysis showed that preoperative HbA1c was predictive only of prolonged inotropic support (AUC 0.542, 95%CI 0.506-0.577). In these patients, HbA1c ≥53 mmol/mol (NGSP units 7.0%) was predictive of postoperative stroke (5.9% vs. 0.8%, adjusted p<0.001, OR 5.677, 95%CI 1.736-18.568) and of prolonged inotropic support (38.8% vs. 22.1%, adjusted p=0.01, OR 1.878, 95%CI 1.165-3.027)

Among patients with diabetes, ROC curve analysis showed that preoperative HbA1c was predictive only of SWI (AUC 0.629, 95%CI 0.562-0.696). HbA1c ≥53 mmol/mol (NGSP units 7.0%) was predictive only of SWI (11.1% vs. 4.8%, adjusted analysis, p=0.002, OR 2.313, 95%CI 1.346-3.973).

3.4. HbA1c and sternal wound infection in patients undergoing single and bilateral internal mammary artery grafting

Among patients undergoing single internal mammary artery grafting, the rates of any SWI (crude rates, HbA1c <53 mmol/mol: 2.4%; 53-75 mmol/mol: 9.0%; > 75 mmol/mol: 13.3%, adjusted p-value: <0.001) as well as deep SWI/mediastinitis (crude rates, HbA1c <53 mmol/mol: 0.9%; 53-75 mmol/mol: 3.2%; > 75 mmol/mol: 5.0%, adjusted p-value: 0.016) increased significantly along with increasing cut-off values of HbA1c.

Among patients undergoing bilateral internal mammary artery grafting, the rates of any SWI (crude rates, HbA1c <53 mmol/mol: 4.1%; 53-75 mmol/mol: 9.6%; >75 mmol/mol: 17.1%, adjusted p-value: 0.002) increased significantly along with increasing cut-off values of baseline HbA1c. A similar difference was observed for deep SWI/mediastinitis (crude rates, HbA1c <53 mmol/mol: 1.7%; 53-75 mmol/mol: 3.3%; >75 mmol/mol: 7.3%, adjusted p-value: 0.170), but it did not reach statistical significance in the adjusted analysis.

Discussion

The present study showed a significant increase in baseline level of HbA1c, particularly among diabetics. This finding is of clinical relevance because poorly controlled diabetes is associated with poor late outcome [18-20]. Increased levels of HbA1c, independently of diabetes, has been demonstrated to increase the risk of late mortality also in patients undergoing CABG [9,21,22]. Therefore, preoperative identification and interventions to optimize glycemic control in such a large number of patients might improve long-term outcome after cardiac surgery.

The present results suggest that only a limited number of patients without a history of diabetes and undergoing elective coronary surgery have a baseline level of Hba1c ≥53 mmol/mol (7.0%) and HbA1c was predictive of stroke and prolonged use of inotropes in this patient group. Indeed, the recent National Institute for Health and Clinical Excellence guidelines do not recommend the preoperative screening of HbA1c in non-diabetic patients undergoing elective surgery [23]. However, these guidelines suggested that preoperative HbA1c measurement could be appropriate in patients that are considered to be at high risk of diabetes [23]. There is scarce evidence on the negative prognostic impact of high levels of preoperative HbA1c in non-diabetics undergoing CABG [24]. Therefore, further studies are needed to evaluate the utility of routine measurement of HbA1c before CABG in patients without history of diabetes.

This study confirmed the findings of a few prior studies demonstrating the ability of preoperative levels of HbA1c to predict SWI after coronary surgery [9-11]. Since this was not an interventional study, the present findings are only hypothesis-generating. However, these results are of clinical significance since hyperglycemia-related infection is a preventable condition [8], particularly in

patients undergoing elective surgery. Indeed, preoperative identification of undiagnosed diabetes or poor diabetes regulation in patients with stable coronary artery disease may allow interventions to optimize diabetes treatment, to postpone surgery until adequate glycemic level are achieved and/or to modify the revascularization strategy. In fact, single internal mammary artery grafting could be indicated in patients with poorly controlled diabetes in order to reduce their risk of SWI, particularly when other risk factors for SWI are present. Furthermore, meticulous surgical wound care and tight monitoring of biomarkers of septicemia [25], may be of benefit for early recognition and prompt treatment of SWI in these high-risk patients.

This study did not show a significant increased risk of early mortality associated with raised HbA1c levels as observed in other series [10,26]. However, this might be owing to the low operative risk of this cohort of elective patients. Prior studies showed an association between high preoperative levels of HbA1c and postoperative acute kidney injury [10,26-29]. The present results suggest that increased HbA1c levels are associated with higher risk of acute kidney injury, but these findings were not confirmed when HbA1c was dichotomized. The mechanisms underlying the development of acute kidney injury in patients with poor glycemic control are not clear, but glycosylation-related changes of the mesangial matrix [30] are most likely to contribute to postoperative acute renal failure in patients with increased HbA1c, independently of estimated glomerular filtration rate and other relevant comorbidities and perioperative events as demonstrated in this analysis.

This study has several limitations. First, this series is likely not powered to estimate the risk of some complications in patients undergoing elective coronary surgery. This limitation is particularly evident for events such as in-hospital mortality and stroke, which are uncommon in these low-risk patients. Still, we believe that the evaluation of this patient population provides important insights for screening and potential treatment of hyperglycemia when surgery could be postponed without incremental risks. Second, the present study is an analysis of data from a prospective registry, but HbA1c was routinely measured only in a few participating centers, whereas in other centers the measurements of this biomarker were scattered. Therefore, the prevalence of poorly controlled glycemia in these series may not reflect its true proportion in patients undergoing elective CABG. Fourth, these results are from patients undergoing elective, isolated CABG and may not be confirmed in patients undergoing

urgent/emergent CABG and/or procedures other than isolated CABG. Fifth, we do not have data on specific diabetes drug regimen, whether diabetes was stable, improving or worsening and on any possible preoperative titration of antidiabetic drugs in these patients. Sixth, HbA1c was not measured in a core laboratory. However, currently this biomarker is measured worldwide using a standardized method which should minimize any interinstitutional differences in this study. Finally, postoperative levels of blood glucose were not recorded in this registry and this prevents a more in-depth analysis of the impact of postoperative glycemia control on the outcomes of these patients. However, HbA1c is a reliable measure of formation of advanced glycation end products, which occurred several weeks before surgery and can affect several immune response pathways [3-5]. In case of excessively high levels of HbA1c, it is unlikely that a tight postoperative control of hyperglycemia might decrease the level of these end-products and reduce the risk of infection.

In conclusion, HbA1c is increased in a significant proportion of patients undergoing elective CABG and these patients are at higher risk of SWI. The impact of HbA1c on postoperative acute kidney injury in these patients is less clear. However, HbA1c seems to be of limited value to predict other outcomes. These results do not support a screening of HbA1c in patients without history of diabetes. Therefore, preoperative screening of HbA1c seems to be of value only in identifying diabetics at high risk of SWI. The potential benefits of preoperative optimization of glycemic control before elective CABG should be evaluated in future trials.

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Table 1. Baseline and operative characteristics in the overall series and in classes of increasing values of baseline HbA1c.

Variables	*Overall series*	*HbA1c <53 mmol/mol 1954 pts*	*HbA1c 53-75 mmol/mol 550 pts*	*HbA1c >75 mmol/mol 102 pts*	*P-value*
Age (years)	67.5±9.1	67.4±9.2	68.4±8.4	65.3±8.4	0.001
Female	365 (14.0)	249 (12.7)	96 (17.5)	20 (19.6)	0.005
Body mass index (kg/ m^2)	27.8±4.3	27.6±4.2	28.5±4.4	28.1±4.6	<0.0001
Hemoglobin (g/L)	140±16	141±15	136±17	137±17	<0.0001
eGFR* (mL/min/1.73 m^2)	76±20	76.6±18.8	74.2±21.2	79.1±21.9	0.005
Dialysis	25 (1.0)	19 (1.0)	5 (0.9)	1 (1.0)	0.991
Diabetes	942 (36.1)	394 (20.6)	461 (86.0)	87 (89.7)	<0.0001
Non-insulin dependent	620 (23.8)	288 (15.1)	285 (53.2)	47 (48.5)	<0.0001
Insulin dependent	322 (12.4)	106 (5.5)	176 (32.8)	40 (41.2)	<0.0001
Stroke	126 (4.8)	88 (4.5)	34 (6.2)	4 (3.9)	0.224
Pulmonary disease	230 (8.8)	162 (8.3)	59 (10.7)	9 (8.8)	0.205
Extracardiac arteriopathy	523 (20.1)	346 (17.7)	147 (26.8)	30 (29.4)	<0.0001
Recent myocardial infarction	234 (9.0)	169 (8.7)	51 (9.3)	14 (13.7)	0.210
Other than prophylactic antibiotics	27 (1.0)	19 (1.0)	7 (1.3)	1 (1.0)	0-827
LVEF ≤50%	655 (25.1)	457 (23.4)	171 (31.1)	27 (26.7)	0.001
BIMA grafting	1159 (44.5)	878 (45.1)	240 (43.6)	41 (40.6)	0.585
EuroSCORE II (%)	1.7±1.8	1.6±1.4	2.2±2.9	2.0±1.7	<0.001

Nominal variables are reported as counts and percentages. Continuous variables are reported mean and standard deviation. *: calculated using the CKD-EPI equation. Abbreviations: eGFR, estimated glomerular filtration rate; BIMA, bilateral internal mammary artery; LVEF, left ventricular ejection fration; EuroSCORE: European System for Cardiac Operative Risk Evaluation.

Table 2. Unadjusted and adjusted areas under the receiver operating receiver curve for HbA1c in predicting postoperative adverse events.

Outcomes	*Unadjusted AUC (95%CI)*	*Adjusted AUC, 95%CI*
Overall cohort		
In-hospital death	0.411, 0.304-0.518	0.375, 0.228-0.521
Any sternal wound infection	**0.664, 0.611-0.716**	**0.652, 0.596-0.708**
Deep sternal wound infection/mediastinitis	**0.636, 0.549-0.723**	**0.618, 0.528-0.708**
Prolonged inotropic support	0.518, 0.492-0.546	0.512, 0.481-0.542
Acute kidney injury of any severity	**0.545, 0.517-0.572**	0.522, 0.490-0.554
Stroke	0.561, 0.432-0.690	0.568, 0.439-0.696

AUC: area under the receiver operating characteristics curve; CI: confidence interval. In bold are statistically significant differences.

Table 3. Adjusted risk estimates of serum levels of HbA1c as a continuous variable in predicting postoperative adverse events.

Outcomes	*Adjusted p-value*	*Odds ratio, 95%CI*
In-hospital death	0.073	0.949, 0.897-1.005
Any sternal wound infection	**<0.001**	**1.036, 1.025-1.047**
Deep sternal wound infection/mediastinitis	**0.003**	**1.026, 1.009-1.044**
Prolonged inotropic support	0.696	1.001, 0.994-1.001
Acute kidney injury of any severity	**0.021**	**1.009, 1.001-1.016**
Stroke	0.313	1.015, 0.986-1.043

CI: confidence interval. In bold are statistically significant differences.

Table 4. Crude rates and adjusted risk estimates of increasing cut-off values of baseline HbA1c in predicting postoperative adverse events.

Outcomes	*Overall series*	*HbA1c <53 mmol/mol 1954 pts*	*HbA1c 53-75 mmol/mol 550 pts*	*HbA1c >75 mmol/mol 102 pts*	*Adjusted p-value*
In-hospital death	17 (0.7)	16 (0.8) Reference	1 (0.2) 0.20, 0.24-1.59	0 0, 0-0	0.312
Any sternal wound infection	128 (4.9)	62 (3.2) Reference	51 (9.3) 2.82, 1.89-4.21	15 (14.7) 4.80, 2.56-9.00	**<0.001**
Deep sternal wound infection/mediastinitis	49 (1.9)	25 (1.3) Reference	18 (3.3) 2.23, 1.17-4.24	6 (5.9) 4.18, 1.61-10.85	**0.003**
Prolonged inotropic support	580 (22.3)	423 (21.7) Reference	130 (23.6) 1.05, 0.83-1.33	27 (26.7) 1.23, 0.76-1.99	0.668
Acute kidney injury	549 (21.5)	381 (19.9) Reference	142 (26.2) 1.20, 0.94-1.52	26 (26.0) 1.46, 0.89-2.38	0.136
Stroke	25 (1.0)	14 (0.7) Reference	9 (1.6) 1.97, 0.78-4.97	2 (2.0) 3.79, 0.79-18.27	0.150

Risk estimates are odds ratios and confidence intervals. Outcomes are reported as counts and percentages. In bold are statistical significant differences.

Highlights

- HbA1c is increased in a significant number of patients undergoing coronary artery bypass grafting
- Preoperative screening of HbA1c is not justified in non-diabetic patients undergoing coronary artery bypass grafting.
- Preoperative screening of HbA1c is of value to identify patients at higher risk of postoperative sternal wound infection after coronary artery bypass grafting.
- Less clear is the impact of increased HbA1c on other postoperative outcomes.