Glycated Hemoglobin and Risk of Sternal Wound Infection After Isolated Coronary Surgery.

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Background: Glycated hemoglobin (HbA1c) is a suspected risk factor for sternal wound infection (SWI) after CABG.

Methods and Results: Data on preoperative HbA1c and SWI were available in 2,130 patients undergoing isolated CABG from the prospective E-CABG registry. SWI occurred in 114 (5.4%). Baseline HbA1c was significantly higher in patients with SWI (mean, 54±17 vs. 45±13 mmol/mol, P<0.0001). This difference was also observed in patients without a diagnosis of diabetes (P=0.027), in insulin-dependent diabetic (P=0.023) and non-insulin-dependent diabetic patients (P=0.034). In the overall series, HbA1c >70 mmol/mol (NGSP units, 8.6%) was associated with the highest risk of SWI (20.6% vs. 4.6%; adjusted OR, 5.01; 95% CI: 2.47–10.15). When dichotomized according to the cut-off 53 mmol/mol (NGSP units, 7.0%) as suggested both for diagnosis and optimal glycemic control of diabetes, HbA1c was associated with increased risk of SWI in the overall series (10.6% vs. 3.9%; adjusted OR, 2.09; 95% CI: 1.24–3.52), in diabetic patients (11.7% vs. 5.1%; adjusted OR, 2.69; 95% CI: 1.38–5.25), in patients undergoing elective surgery (9.9% vs. 2.7%; adjusted OR, 2.09; 95% CI: 1.24–3.52) and in patients with bilateral mammary artery grafts (13.7% vs. 4.8%; adjusted OR, 2.35; 95% CI: 1.17–4.69).

Conclusions: Screening for HbA1c before CABG may identify untreated diabetic patients, as well as diabetic patients with suboptimal glycemic control, at high risk of SWI.

Key Words: Coronary artery bypass grafting; Glycated hemoglobin; Hemoglobin A1c; Sternal wound infection

P atients with diabetes mellitus are at increased risk of infection.[1] The mechanisms underlying this susceptibility to infectious diseases are not completely understood, but the evidence suggests that hyperglycemia results in formation of advanced glycation end products, which can affect host cell function by impairing humoral response, complement activation, chemotaxis, adhesion and phagocytosis as well as intracellular and extracellular

killing.[2-4] These defects seem to be reversed by optimization of glycemic control.[5] As a consequence, diabetic patients are at increased risk of surgical site infection, and such a risk seems to be highest in patients undergoing cardiac surgery.[6] The efficacy of tight perioperative glycemic control in reducing the risk of surgical site infection, however, remains controversial.[7,8] Failure to reduce the risk of surgical site infection by optimal perioperative insulin treatment may be due to poor preoperative glycemic control, which affects immunity and therefore the susceptibility to infection in patients undergoing surgery. Hyperglycemia induces also the irreversible formation of glycated hemoglobin or hemoglobin A1c (HbA1c), which is eliminated only at the end of the red blood cell lifespan and therefore allows an assessment of the glycemic control during a 3–4-month period.[9,10] A few reports suggest that increased preoperative HbA1c is a predictor of sternal wound infection (SWI) in patients undergoing coronary artery bypass grafting (CABG).[11,12] The purpose of the present study was therefore to investigate the prevalence of increased HbA1c and its impact on the development of SWI in patients undergoing isolated CABG, using a prospective, multicenter registry.

Methods

Subjects
The E-CABG registry is a prospective registry enrolling 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). Twelve of these centers were university hospitals, 2 centers were central hospitals and 2 centers were private hospitals with agreements with the regional health authorities. Data on baseline, intraoperative and postoperative variables were prospectively collected in an Access datasheet by researchers who were specifically trained for data collection into this registry. Data were checked by researchers from each participating center before submission of the 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) and its detailed protocol and definition criteria have been published previously.[13]

Out of 3,788 consecutive patients enrolled in the E-CABG registry, 2,130 patients who underwent surgery between January 2015 and February 2016, had baseline HbA1c and blood glucose measured at hospital admission for the index procedure and comprised the subjects of the present analysis. A moderate or liberal approach to perioperative glycemic control was adopted in these patients. None of the participating centers adopted a tight perioperative glycemic control policy.

Outcome Measures
The primary outcome of this study was SWI of any severity. Secondary outcomes were type of SWI, that is, superficial wound infection, deep wound infection and mediastinitis. The diagnosis and severity of SWI were defined and graded according to the Centers for Disease Control and Prevention classification of the surgical site infections.[14] Thirty-day and 6-month mortality were also considered as secondary outcomes.

Ethics
This study was approved by the Regional Ethics Review Board or Institutional Review Board of each participating center. Informed consent was collected in institutions where it was required by the Review Board, otherwise it was waived. This study was not financially supported.

Statistical Analysis
Statistical analysis was performed using SPSS v. 23.0 (IBM, Armonk, NY, USA). No attempt to replace missing values was made. Continuous variables are reported as mean±SD. Nominal variables are reported as n (%). Fisher's exact test, chi-squared test, Mann-Whitney test and Spearman test were used for univariate analysis. HbA1c is mainly reported as mmol/mol according to the International Federation of Clinical Chemistry units, but HbA1c cut-offs are reported 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 the cut-off 53mmol/mol (NGSP units, 7.0%), as suggested both for diagnosis and optimal glycemic control of diabetes.[10] Classification and regression tree (CART) analysis was performed to estimate an appropriate cut-off of HbA1c in predicting SWI. The risk estimate of SWI was adjusted in logistic regression models for differences in their characteristics using 2 methods: (1) inclusion of the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) as a covariate;[15] and (2) inclusion of the following baseline, operative and bleeding covariates with P<0.05 on univariate analysis in the regression model: gender, body mass index (BMI), hemoglobin, HbA1c, C-reactive protein ≥10mg/dL, estimated glomerular filtration rate, antibiotics other than for prophylaxis, diabetes on treatment, poor mobility, extracardiac arteriopathy, recent myocardial infarction, non-elective surgical priority, bilateral internal thoracic artery use, length of operation and total number of units of transfused red blood cells. Mediastinal re-exploration for excessive bleeding was forced into the regression models. Logistic regression was then performed with the backward stepwise elimination method in order to identify the risk factors for postoperative SWI. The predictive ability of the regression models as well as of continuous variables to predict SWI was evaluated using the receiver operating characteristic curve and calculation of the area under the curve (AUC). Survival analysis was performed using the Kaplan-Meier and the Cox proportional hazards methods. All tests were 2-sided with the α level set at 0.05 for statistical significance.

Results

Patient characteristics, operative variables and bleeding-related data are summarized in **Tables 1,2**. Of the 2,130 patients included in the present analysis, 466 (21.9%) were non-insulin-dependent diabetic patients with on-going oral treatment and 280 (13.1%) were insulin-dependent diabetic patients. In the overall series, HbA1c was >53mmol/mol (NGSP units, 7.0%) in 461 (21.6%), of whom 392 (52.5%) were diabetic and 69 (5.0%) were non-diabetic. Elective surgery was performed in 1,386 patients (65.1%; **Table 1**). Both internal mammary arteries were harvested in 907

Table 1. Baseline Subject Characteristics vs. Presence of SWI

Baseline variables	Overall series (n=2,130)	No SWI (n=2,016)	SWI (n=114)	P-value
Age (years)	67.5±9.2	67.5±9.2	69.1±9.3	0.054
Female	356 (16.7)	327 (16.2)	29 (25.4)	0.010
BMI (kg/m²)	27.8±4.3	27.7±4.2	29.3±5.1	<0.0001
Hemoglobin (g/L)	137±16	137±16	131±18	<0.0001
Anemia	448 (21.0)	412 (20.4)	36 (31.6)	0.005
HbA1c (mmol/mol)	46±13	45±13	54±17	<0.0001
eGFR (mL/min/1.73 m²)	80±25	80±25	74±29	0.009
CKD classes				<0.0001
3A	275 (12.9)	254 (12.6)	21 (18.6)	
3B	102 (4.8)	91 (4.5)	11 (9.7)	
4	26 (1.2)	20 (1.0)	6 (5.3)	
5	21 (1.0)	19 (0.9)	2 (1.8)	
CRP ≥10 mg/dL†	389 (19.8)	358 (19.2)	31 (30.7)	0.005
Antibiotics other than prophylaxis	57 (2.7)	50 (2.5)	7 (6.1)	0.018
Chronic lung disease	190 (8.9)	177 (8.8)	13 (11.4)	0.339
Diabetes on treatment	746 (35.1)	682 (33.8)	64 (56.6)	<0.0001
Insulin dependent	280 (13.2)	247 (12.3)	33 (29.2)	<0.0001
Non-insulin dependent	466 (21.9)	435 (21.6)	31 (27.4)	0.16
Stroke	109 (5.1)	103 (5.1)	6 (5.3)	0.942
Poor mobility	55 (2.6)	46 (2.3)	9 (7.9)	<0.0001
Extracardiac arteriopathy	435 (20.4)	403 (20.0)	32 (28.1)	0.037
Atrial fibrillation	180 (8.5)	166 (8.3)	14 (12.4)	0.126
Prior PCI	483 (22.7)	461 (22.9)	22 (19.3)	0.376
Prior cardiac surgery	17 (0.8)	15 (0.7)	2 (1.8)	0.238
LVEF (%)				0.815
31–50	498 (23.4)	468 (23.3)	30 (26.3)	
21–30	86 (4.0)	82 (4.1)	4 (3.5)	
<21	11 (0.5)	10 (0.5)	1 (0.9)	
Recent MI	504 (23.7)	463 (23.0)	41 (36.0)	0.001
Coronary artery disease				
Left main disease	730 (34.3)	682 (33.8)	48 (41.7)	0.083
No. diseased vessels	2.7±0.6	2.7±0.6	2.7±0.5	0.998
Syntax score	28.7±10.1	28.7±10.1	29.8±10.3	0.117
Non-elective operation	744 (34.9)	689 (34.2)	55 (48.2)	0.002
Critical state	83 (3.9)	75 (3.7)	8 (7.0)	0.077
GRACE in-hospital death score (%)	2.4±4.1	2.3±3.8	4.2±6.9	<0.0001
EuroSCORE II (%)	2.5±3.8	2.5±3.8	3.5±3.7	<0.0001

Data given as mean±SD or n (%). †Data available from 1,961 patients. BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GRACE, Global Registry of Acute Coronary Events; HbA1c, hemoglobin A1c; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SWI, sternal wound infection.

patients (42.6%; **Table 2**).

SWI

A total of 114 patients (5.4%) had SWI. Superficial wound infection occurred in 59 (2.8%), deep wound infection in 40 (1.9%), and mediastinitis in 15 (0.7%). The incidence of SWI ranged from 0 to 16.7% between different centers (P=0.005), but this difference was not statistically significant when adjusted for baseline HbA1c and other covariates with P<0.05 on univariate analysis (adjusted P=0.484). A diagnosis of SWI was made after a mean interval of 19.5±17.1 days (median, 15 days) from surgery. Thirty-day mortality was higher in those patients with SWI (2.6 vs. 1.3%, P=0.200), but the difference did not reach statistical

significance. SWI was, however, associated with a significantly higher 6-month mortality compared with the patients without SWI (7.4% vs. 2.2%, log-rank P<0.0001, adjusted for EuroSCORE II: HR, 3.959; 95% CI: 1.820–8.616).

Baseline HbA1c and Risk of SWI

Baseline HbA1c was higher in patients with SWI than in those without SWI (mean, 54±17 vs. 45±13 mmol/mol, P<0.0001; **Table 1**). This difference was observed in patients with insulin-dependent diabetes (mean, 64.5±16.4 vs. 58.9±16 mmol/mol, P=0.023), in those with non-insulin-dependent diabetes (mean, 60.3±15.7 vs. 54.1±11.7 mmol/mol, P=0.034) and in those without a preoperative diagnosis of

Table 2. Operative Data and Postoperative Bleeding-Related Variables

Operative variables	Overall series (n=2,130)	No SWI (n=2,016)	SWI (n=114)	P-value
Antibiotic prophylaxis				<0.0001
Cefuroxime	1,024 (48.1)	975 (48.4)	49 (42.6)	
Cefazoline	580 (27.2)	546 (27.1)	34 (29.6)	
Cloxacillin+teicoplanin	200 (9.4)	194 (9.6)	6 (5.3)	
Cefazoline+teicoplanin	171 (8.0)	168 (8.3)	3 (2.6)	
Cefamandole	57 (2.7)	50 (2.5)	7 (6.1)	
Amoxicillin	32 (1.5)	27 (1.3)	5 (4.3)	
Vancomycin	19 (0.7)	14 (0.7)	5 (4.3)	
Ceftriaxone	15 (0.7)	15 (0.7)	0	
Cefazoline+vancomycin	11 (0.5)	10 (0.5)	1 (0.9)	
Other antibiotics	4 (0.2)	4 (0.2)	0	
Missing information	11 (0.5)	8 (0.4)	3 (2.6)	
Operative variables				
Off-pump technique	548 (25.7)	523 (26.0)	25 (21.9)	0.340
Single internal thoracic artery use	1,188 (55.8)	1,137 (56.4)	51 (44.7)	0.015
Bilateral internal thoracic artery use	907 (42.6)	846 (42.0)	61 (53.5)	0.015
No. distal anastomoses	2.8±1.0	2.8±1.0	2.8±1.0	0.422
Aortic cross-clamping time (min)	61±36	60±36	63±30	0.152
CPB time (min)	84±36	84±36	86±37	0.388
Length of operation (min)	231±75	230±75	256±68	<0.0001
Bleeding-related variables				
12-h chest tube output (mL)	460±313	459±312	478±334	0.950
Nadir Hb (g/L)	97±16	97±16	93±15	0.023
RBC transfusion	827 (38.8)	758 (37.6)	69 (60.5)	<0.0001
Intraoperative RBC (units)	0.3±0.8	0.3±0.8	0.5±0.8	<0.0001
Perioperative RBC (total units)	1.1±2.2	1.0±2.2	2.0±2.9	<0.0001
FFP/Octaplas transfusion	125 (5.9)	115 (5.7)	10 (8.8)	0.175
Platelets transfusion	167 (7.8)	159 (7.9)	8 (7.0)	0.737
Reoperation for bleeding	68 (3.2)	62 (3.1)	6 (5.3)	0.196
E-CABG bleeding grade 2–3[†]	128 (6.0)	111 (5.5)	17 (14.9)	<0.0001

Data given as mean±SD or n (%). [†]Transfusion >4 units RBC and/or reoperation for excessive bleeding. CPB, cardiopulmonary bypass; E-CABG, European Coronary Artery Bypass Grafting Registry; FFP, fresh frozen plasma; Hb, hemoglobin; RBC, red blood cell; SWI, sternal wound infection.

diabetes (mean, 42.3±8.6 vs. 39.8±7.9 mmol/mol, P=0.027; **Figure 1**). Rate of SWI and severity of infections according to baseline HbA1c quintile is given in **Figure 2**.
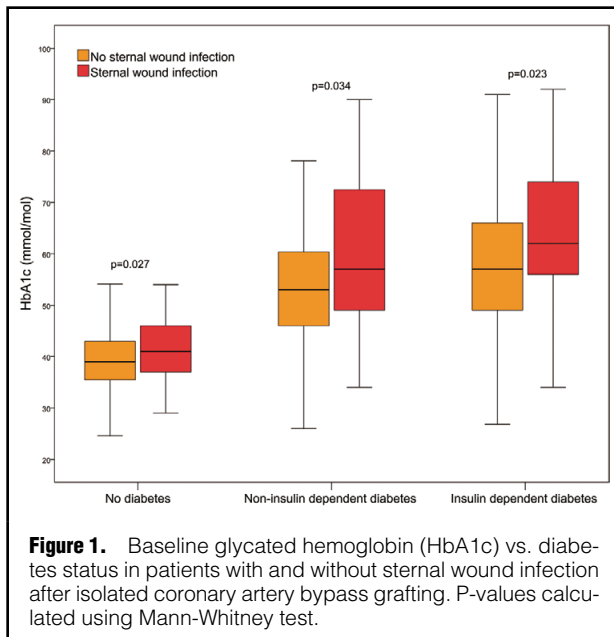
Baseline blood glucose was increased in patients with SWI (P=0.014; **Table 1**) and there was a positive correlation between baseline blood glucose and HbA1c (rho=0.51, P<0.0001). The AUC for prediction of SWI was 0.66 (95% CI: 0.60–0.71) for baseline HbA1c and 0.57 (95% CI: 0.51–0.63) for baseline blood glucose. On logistic regression modeling including both HbA1c and blood glucose, only HbA1c was associated with increased risk of SWI. Because of these findings, blood glucose was included in all adjusted analyses but further specific analyses on this variable were not performed.

On logistic regression modeling (Hosmer-Lemeshow test, P=0.52; AUC, 0.75; 95% CI: 0.71–0.80) including HbA1c as a continuous variable, this variable was an independent risk factor for SWI (OR, 1.04; 95% CI: 1.02–1.05, P<0.0001; **Table 3**).

CART analysis identified baseline HbA1c=70 mmol/mol (NGSP units, 8.6%; prevalence in the overall series, 4.7%) as the most accurate cut-off for prediction of SWI. Patients with HbA1c >70 mmol/mol had a rate of SWI of 20.6%,

compared with 4.6% in those with lower HbA1c (P<0.0001, crude OR, 5.39; 95% CI: 3.20–9.10). Similarly, among diabetic patients, HbA1c >70 mmol/mol was associated with an increased risk of SWI (21.3% vs. 6.7%, P<0.0001, crude OR, 3.74; 95% CI: 2.09–6.68). HbA1c >70 mmol/mol was an independent predictor of SWI also when adjusted for EuroSCORE II (OR, 3.68; 95% CI: 2.04–6.55) and for covariates with P<0.05 on univariate analysis (OR, 4.39; 95% CI: 2.31–8.34). No significant differences were observed between centers (adjusted P=0.372). The rates of superficial wound infection, deep wound infection and mediastinitis in patients with HbA1c>70 mmol/mol were 14.7%, 2.9% and 2.9%, respectively, whereas in those with lower HbA1c they were 2.2%, 1.8% and 0.6%, respectively (P<0.0001).

When HbA1c was dichotomized according to the suggested cut-off of ≤53 and >53 mmol/mol as suggested both for diagnosis and optimal glycemic control of diabetes,[10] the rates of superficial wound infection, deep wound infection and mediastinitis were 7.2%, 2.4% and 1.1%, respectively, in patients with HbA1c >53 mmol/mol (NGSP units, 7.0%) and 1.6%, 1.7% and 0.6%, respectively in those with lower HbA1c (P<0.0001). On logistic regression
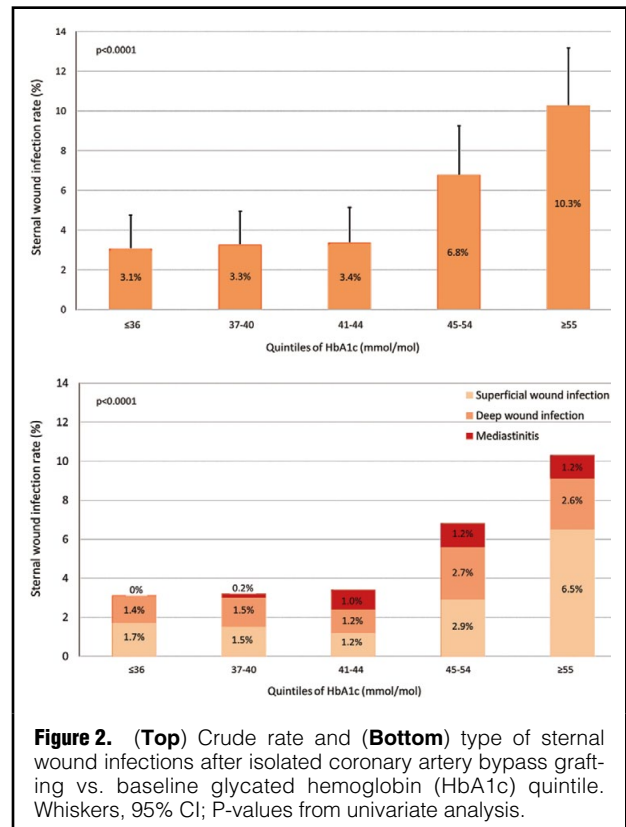
Figure 1. Baseline glycated hemoglobin (HbA1c) vs. diabetes status in patients with and without sternal wound infection after isolated coronary artery bypass grafting. P-values calculated using Mann-Whitney test.

Figure 2. (**Top**) Crude rate and (**Bottom**) type of sternal wound infections after isolated coronary artery bypass grafting vs. baseline glycated hemoglobin (HbA1c) quintile. Whiskers, 95% CI; P-values from univariate analysis.

(Hosmer-Lemeshow test, P=0.193; AUC, 0.76; 95% CI: 0.71–0.80), HbA1c >53 mmol/mol (NGSP units, 7.0%), was associated with an increased risk of SWI (OR, 2.15; 95% CI: 1.28–1.96, P=0.004; **Table 3**). No significant differences were observed between centers (adjusted P=0.427).

Sensitivity Analysis

Table 4 summarizes the results of adjusted analyses on the impact of HbA1c >53 mmol/mol (NGSP units, 7.0%) on the development of SWI in different subsets of patients. This cut-off was an independent predictor of surgical site infection in the overall series, in patients on treatment for diabetes, in those undergoing elective procedures as well as in those in whom both internal mammary arteries were harvested. HbA1c >53 mmol/mol (NGSP units, 7.0%), however, was not associated with an increased risk of SWI in non-diabetic patients (P=0.712). Furthermore, in patients receiving only 1 internal mammary artery graft, the prognostic value of this cut-off was confirmed on univariate analysis (P<0.0001) and EuroSCORE II adjusted analysis (P<00001), but not on multiple covariate-adjusted analysis (P=0.232).

Prognostic Value of HbA1c in Non-Diabetic Patients

Among non-diabetic patients, the AUC for HbA1c in predicting SWI was 0.59 (95% CI: 0.51–0.68). According to HbA1c quintile in non-diabetic patients, the rate of SWI was significantly higher only in the highest HbA1c quintile (<35 mmol/mol, 2.3%; 35–37 mmol/mol, 3.7%; 38–40 mmol/mol, 2.5%; 41–44 mmol/mol, 3.2%; and >44 mmol/mol, 6.9%, P=0.037). This was confirmed at multivariate analysis adjusted for EuroSCORE II (for the highest quintile: OR, 3.143; 95% CI: 1.27–7.79, P=0.013) and on multiple covariate-adjusted analysis (for the highest quintile: OR, 2.712; 95% CI: 1.01–7.32, P=0.049). HbA1c >44 mmol/mol (NGSP >6.2%) was associated with a significantly higher risk of SWI in non-diabetic patients compared with lower HbA1c on univariate analysis (6.9% vs. 2.9%, P=0.002). When logistic regression with back-

ward selection was used, HbA1c >44 mmol/mol was an independent predictor of SWI (OR, 2.228; 95% CI: 1.172–4.237; P=0.012) along with BMI (OR, 1.082, 95% CI: 1.014–1.153; P=0.017), baseline hemoglobin (OR, 0.980; 95% CI: 0.962–0.998; P=0.027), recent myocardial infarction (OR, 2.343; 95% CI: 1.267–4.334; P=0.008) and length of operation (per 10-min increase: OR, 1.073; 95% CI: 1.034–1.115; P<0.0001).

Discussion

This study noted a relatively low incidence of SWI, despite the particularly frequent use (42.6%) of bilateral internal mammary artery grafts in this series. Furthermore, half of the SWI were superficial and 13% of these patients had mediastinitis. The occurrence of SWI, however, translated into a higher 6-month mortality, which confirms the severity of this condition and the need for measures to prevent it.

The present results confirmed that preoperative HbA1c is an independent predictor of surgical site infection after cardiac surgery in diabetic patients and in patients with previously undiagnosed diabetes.[11,12,16] Baseline HbA1c >70 mmol/mol (NGSP units, 8.6%) was associated with the higher risk of SWI. Interestingly, in this series, one-fifth of patients undergoing isolated CABG had HbA1c >53 mmol/mol (NGSP units, 7.0%), which is a recognized marker of poor glycemic control.[10] The prevalence of suboptimal HbA1c level was 52.5% in diabetic patients, and was also detected in 5% of patients without preoperative diagnosis of diabetes. Beside the observation of increased risk of SWI among patients with increased HbA1c, these figures indicate the importance of HbA1c screening in all

Table 3. Independent Predictors of SWI on Logistic Regression Modeling

Covariates	B-coefficient	P-value	OR, 95% CI
HbA1c as a continuous variable			
Baseline HbA1c	0.035	<0.0001	1.035, 1.023–1.048
BMI	−0.088	<0.0001	1.092, 1.046–1.140
Baseline Hb	−0.015	0.013	0.985, 0.973–0.997
Poor mobility	0.900	0.032	2.460, 1.083–5.589
Urgent/emergency procedure	0.511	0.019	1.667, 1.088–2.555
Bilateral mammary artery grafts	0.589	0.011	1.803, 1.147–2.834
RBC units transfused	0.087	0.003	1.091, 1.029–1.156
Constant	−6.549		
HbA1c with a cut-off of >53 mmol/mol			
Baseline HbA1c >53 mmol/mol†	0.676	0.004	2.153, 1.284–1.958
BMI	0.078	<0.0001	1.081, 1.035–1.129
Baseline Hb	−0.014	0.031	0.987, 0.977–0.999
Poor mobility	0.912	0.030	2.488, 1.091–5.675
Bilateral mammary artery grafts	0.504	0.028	1.655, 1.055–2.597
Length of operation (per 10-min increase)	0.029	0.051	1.029, 1.000–1.059
RBC units transfused	0.092	0.003	1.097, 1.032–1.165
Urgent/emergency procedure	0.540	0.014	1.717, 1.116–2.641
Diabetes		0.065	
Non-insulin dependent	0.070	0.821	1.072, 0.587–1.958
Insulin dependent	0.642	0.004	1.901, 1.044–3.462
Constant	−5.053		

†National Glycohemoglobin Standardization Program units, 7.0%. Abbreviations as in Tables 1,2.

Table 4. Impact of HbA1c >53 mmol/mol† on the Development of SWI

	HbA1c ≤53 mmol/mol	HbA1c >53 mmol/mol	P-value	OR, 95% CI
Overall series	1,669 patients	461 patients		
SWI rate	65 (3.9)	49 (10.6)	<0.0001	
EuroSCORE II adjusted			<0.0001	2.93, 1.98–4.34
Multiple covariate-adjusted			0.006	2.09, 1.24–3.52
Non-diabetic patients	1,313 patients	69 patients		
SWI rate	46 (3.5)	3 (4.3)	0.712	
EuroSCORE II adjusted			0.795	1.18, 0.35–3.96
Multiple covariate-adjusted			0.919	0.94, 0.27–3.22
Diabetes on treatment	354 patients	392 patients		
SWI rate	18 (5.1)	46 (11.7)	0.001	
EuroSCORE II adjusted			0.002	2.44, 1.38–4.30
Multiple covariate-adjusted			0.004	2.69, 1.38–5.25
Elective operation	1,084 patients	302 patients		
SWI rate	29 (2.7)	30 (9.9)	<0.0001	
EuroSCORE II adjusted			<0.0001	3.97, 2.31–6.82
Multiple covariate-adjusted			0.009	2.67, 1.28–5.57
Single IMA graft	928 patients	260 patients		
SWI rate	29 (3.1)	22 (8.5)	<0.0001	
EuroSCORE II adjusted			<0.0001	2.96, 1.64–5.32
Multiple covariate-adjusted			0.232	1.69, 0.97–3.97
Bilateral IMA grafts	710 patients	197 patients		
SWI rate	34 (4.8)	27 (13.7)	<0.0001	
EuroSCORE II adjusted			<0.0001	2.99, 1.75–5.12
Multiple covariate-adjusted			0.016	2.35, 1.17–4.69

Data given as n (%). †National Glycohemoglobin Standardization Program units, 7.0%. IMA, internal mammary artery. Other abbreviations as in Tables 1,2.

patients, that is, non-diabetic patients, undergoing cardiac surgery because unrecognized diabetes and poor glycemic control may have immediate and long-term prognostic implications in both diabetic and non-diabetic patients.[16–18]

On multivariate analysis in the total group, increased baseline HbA1c was one of the most powerful predictors of SWI (**Table 3**), and this finding assumes clinical importance given that poor glycemic control could be effectively treated in a large number of patients before surgery. In fact, 22% of patients scheduled for elective CABG had baseline HbA1c >53 mmol/mol (**Table 4**). Among patients who underwent bilateral mammary artery grafting, 22% had baseline HbA1c >53 mmol/mol, resulting in an excessive rate of SWI (13.7% vs. 4.8%, P<0.0001). Furthermore, in non-diabetic patients a lower HbA1c threshold has been identified as a prognostic marker of increased risk of SWI. This requires much attention in order to reduce the high risk of surgical site infection, but also to identify patients who may benefit from diabetes treatment after surgery.

This was an observational study and therefore does not provide definitive evidence of the potential efficacy of preoperative optimization of glycemic control in reducing the risk of SWI. It has, however, shown that a number of modifiable risk factors underlie the development of SWI, which can be targets for prevention of this severe complication. Improved patient blood management and meticulous surgical hemostasis may reduce exposure to blood products and their associated increased risk of infection.[19] Importantly, surgeons should carefully evaluate the harms and benefits of using bilateral internal mammary artery grafts in patients with poor preoperative glycemic control. The present results suggest that the risk of SWI can be prohibitive in patients with high baseline HbA1c and bilateral internal mammary artery grafting. In these high-risk patients, the use of only one internal mammary graft should be considered to minimize sternal ischemia. This strategy may decrease also the duration of surgery and reduce the surgical area at risk of perioperative bleeding. This surgical policy could be particularly wise in the presence of obesity. Knowledge of increased baseline HbA1c may guide the clinicians to adopt a number of further measures to avoid this infectious complication such as dressing of the sternal wound during surgery, rigorous monitoring and aseptic handling of the sternal wound, prophylactic use of incisional negative pressure wound devices, and prompt antibiotic treatment at the first signs of infection.

Study Limitations

A number of limitations should be acknowledged. First, this was a non-consecutive series of patients because HbA1c was not measured routinely in all centers. Furthermore, HbA1c was likely not measured in patients referred from other centers on an emergency basis. Therefore, the herein observed proportion of increased HbA1c and SWI may not reflect the true prevalence of this condition. Second, HbA1c was not measured in a core laboratory and this may introduce a bias due to possible differences in the analyzers, but, because of the clinical relevance and widespread use of HbA1c screening in patients with diabetes and at risk for pre-diabetes, the results have undergone a process of standardization. Third, a number of genetic and acquired conditions as well as drugs may interfere with HbA1c results and cause inappropriately high or low HbA1c measurements. These factors were not taken into account in this analysis. Fourth, only preoperative blood glucose level was considered in this study and neither intraoperative nor postoperative blood glucose were available for analysis. Consequently, it was not possible to confirm whether perioperative hyperglycemia might have been associated with SWI. It is unlikely, however, that intensive perioperative glycemic control may be effective to reverse the effects of advanced glycosylation end products and to improve in such a short time the host response to bacterial infection. Once advanced glycosylation end products are formed, they are nearly irreversible and their effects are likely not short term,[20] or at least do not vanish within a few days from optimization of glycemic control. Fifth, stratification into stable, improving and worsening diabetes would be of importance for a proper definition of glycemic control status in diabetic patients, but this was not feasible in this series because we did not have data on HbA1c before admission for CABG. Finally, this was not an interventional study and therefore does not provide definitive evidence of the potential efficacy of preoperative and perioperative optimization of glycemic control in reducing the risk of SWI. Knowledge of increased baseline HbA1c, however, may guide the clinicians to start or modify anti-diabetic treatment preoperatively, to postpone surgery when feasible until better glycemic control is achieved, and to adopt a number of local wound care measures to prevent and promptly treat this severe infectious complication.

Conclusions

Preoperative screening of HbA1c before isolated CABG may identify a significant number of patients with poor glycemic control, who are at high risk of SWI. Patients without previously diagnosed diabetes are also at increased risk of SWI when baseline HbA1c is increased. Preoperative identification of untreated diabetes, optimization of glycemic control and meticulous wound care may reduce the risk of SWI risk in these patients.

Disclosures

The authors declare no conflicts of interest.

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