ORIGINAL ARTICLE

Glycosylated hemoglobin and adverse events following elective coronary bypass revascularization

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Koechlin L, Schurr U, Gahl B, et al. Glycosylated hemoglobin and adverse events following elective coronary bypass revascularization. Curr Res Cardiol 2018;5(2):18-22.

BACKGROUND: The aim of this retrospective study was to evaluate whether the level of preoperative glycosylated hemoglobin (HbA1c) is associated with incidence of major adverse events in patients undergoing elective coronary bypass surgery.

METHODS: This was a retrospective observational study of 1,116 patients undergoing elective, isolated aortocoronary bypass surgery over a period of 5 years. Two groups were investigated, one with a preoperative HbA1c level ≤6.5% and the other with HbA1c superior to 6.5%. We used propensity modelling to calculate inverse probability of treatment weights (IPTW) for quantifying the association of increased HbA1c on outcome.

RESULTS: According to inclusion criteria, 589 patients (mean age, 68.1 years; female:14%) were included in the analysis. HbA1c was ≤ 6.5% in 410 patients (69.6%) and was higher than 6.5% in 179 patients (30.4%). The in-hospital mortality rate before and after IPTW was not significantly higher in HbA1c>6.5% groups (1.0% vs. 3.4% p=0.054 and 1.1% vs. 3.5% p=0.076). After IPTW, the risk for major cardiovascular events was higher in patients with HbA1c>6.5%, odds ratio [OR] 3.19, confidence interval [CI] 1.48 to 6.87, p=0.003, and the risk for sternal infection OR 8.07 (CI 2.79-23.39, p<0.001), for sepsis OR 5.36 (CI 1.56 -18.46, p=0.008), and renal failure OR 3.16 (CI 1.12-8.88, p=0.03).

CONCLUSION: Preoperatively, inadequately-treated diabetes mellitus that may be expressed as elevated HbA1c, which is directly associated with an elevated incidence of adverse events following elective coronary revascularization surgery.

Key Words: Glycosylated hemoglobin; Cardiovascular adverse events; Elective coronary bypass surgery

INTRODUCTION

The association between diabetes mellitus (DM) and adverse events following coronary bypass revascularization is well known and as such is a subject of ongoing clinical evaluation. The prevalence of DM in western countries is rising and estimated at between 6 to 10% (1). These estimates reflect the peak of an iceberg and around 20% of DM remains undiagnosed (2). There are many reports revealing the link between DM and postoperative mortality and morbidity, as well as reduced long-term survival following coronary bypass surgery (3-5). Consequently, measures have been introduced to ensure an optimal glycaemia level during intervention and at the early postoperative period in order to improve the short- as well the long-term outcome (6). The importance of maintaining an optimal glucose level in the perioperative period is well accepted; however, the impact of suboptimal diabetes treatment has not been fully investigated. Most studies on diabetes and its impact on outcome only categorize patients into diabetic vs. non-diabetic (5), insulin dependent vs. non-insulin dependent (7), or by the type of the diabetes as diabetes type I vs. type II (4).

Although glycosylated hemoglobin (HbA1c) is considered as one of the best markers to assess glycaemia treatment over a period of 3 to 4 months and is considered a predictive marker for perioperative mortality and morbidity, there are only a handful of reports in the recent literature evaluating suboptimal glycaemia treatment on outcome post coronary-bypass surgery (8). The aim of this retrospective study was to evaluate the impact of elevated HbA1c on incidence of perioperative adverse events in patients undergoing elective coronary bypass surgery.

MATERIALS AND METHODS

This retrospective study looked at 1,116 consecutive patients being operated on for isolated elective coronary bypass revascularization (CABG) between 2012 and 2017. The local ethical committee at Basel University approved the study protocol. Patients undergoing emergency intervention, those with a history of previous surgical interventions, and patients undergoing any concomitant procedure were not considered for evaluation. Independently of diabetes mellitus treatment, two patient groups were stratified. The first group had an elevated preoperative HbA1c level of >6.5% and were mostly patients with treated diabetes mellitus and those without diagnosed diabetes. The second group had HbA1c ≤ 6.5% level and included patients without diabetes and patients with well controlled diabetes. The HbA1c cut-off level was chosen inferior to the recommended target level of 7.0%, (9) in order to obtain results that included those provided with long-term diabetes therapy.

Out of 1,116 patients, 589 (52.78%) had their HbA1c assessed 24 hours prior to intervention and were considered as eligible for the analysis. Both patient groups (HbA1c>6.5% vs. HbA1c≤6.5%) were compared in regard to demographic data, surgical intervention, and coronary vessel pathology, as well as for early morbidity and mortality. Preoperative risk stratification was according to the European System for Cardiac Operative/Central Neurological Event or Stroke and was determined as local and/or global dysfunction for more than 24 hours. Renal dysfunction was defined as elevation of the creatinine level by more than 50% as compared to the baseline value and renal failure was determined as renal dysfunction requiring renal replacement therapy. Myocardial infarction was defined as

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Received: May 17, 2018, Accepted: Jul 25, 2018, Published: Jul 28, 2018

a new Q wave and/or disappearance of the R wave on electrocardiogram or a troponin T level ≥3.9 μg/l in the first 24 h following the intervention (10). A major cerebrovascular or cardiovascular event (MACCE) in the postoperative period was defined as a combined event of new myocardial infarction, stroke and cardiac related death. Wound infection as well sternal infections were diagnosed according to the Center of Disease Control and Prevention definition. Sepsis is defined as Systemic Inflammatory Response Syndrome (SIRS) with evidence of infection in microbiological investigation; Multiple Organ Failure (MOF) was defined as failure of at least two organ systems for at least 24 hours (11). Primary endpoints were defined as in-hospital mortality, myocardial infarction, stroke and MACCE. Secondary endpoints were determined as renal failure, need for renal substitution therapy, sepsis, sternal infection, wound infection and pulmonary infection.

Glycaemia management

Preoperatively, the glucose level was kept under 180 mg/dL. If acquired, oral antidiabetic agents were stopped 48 hours before surgery and were replaced by subcutaneous insulin therapy in order to maintain glucose levels at under 180 mg/dL. Consequently, in theater, the glycaemia level was analysed in samples of arterial blood gases measured in 30-minute periods. In the early postoperative period the glucose level on the intensive care unit was determined every 2 hours. A blood glucose level higher than 180 mg/dL was treated with insulin infusion. In the postoperative period on the surgical ward, the blood glucose level was determined every 4 to 6 hours, and hyperglycemia was treated with subcutaneous insulin if required. Newly diagnosed and poorly controlled diabetes were reviewed by an endocrinologist.

STATISTICAL METHODS

We used propensity modelling to construct sub-cohorts of patients with HbA1c ≤6.5% and HbA1c >6.5% that were similar with respect to pre-operative risk factors for MACCE. We included age, female gender, diseased coronary arteries, main stem stenosis, hypercholesterolemia, NYHA III or IV, current smoker and left ventricular ejection fraction (LVEF) in the propensity model. Tails were trimmed at both ends of the propensity distribution in both groups at the more centered 2.5th or 97.5th percentile, respectively, as these are areas of suspected residual confounding. The inverse probability of treatment weighting (IPTW) was included into the analysis. We derived standardized differences between groups before and after IPTW by dividing differences of proportions and differences of means by the pooled SD, thus expressing all differences in SD units. A 0.10 SD unit difference indicates the smallest potentially meaningful difference between groups (12). All tests and confidence intervals were two-sided and p values <0.05 were deemed to indicate statistically significant differences. Continuous variables were summarized as mean and SD, dichotomous variables were expressed as absolute numbers and percentages, and comparisons were made using a Chi square test. Comparison of prognostic performance of diabetes and Hb1Ac >6.5% was done by first including diabetes as independent binary variable into a logistic regression with the outcome as dependent variable and then adding Hb1Ac >6.5%. We then used the likelihood ratio test to determine whether the increase in likelihood was significant. As a sensitivity analysis, we calculated the likelihood ratio test, when diabetes was added to Hb1Ac >6.5% as independent variable. Association between bilateral internal mammary artery usage and incidence of sternal infection was investigated by logistic regression model, first crude and then adjusted for HbA1c. All statistical analyses were performed by a biostatistician (BG) using Stata 14.0 (StataCorp, College Station, TX, USA).

RESULTS

According to the inclusion criteria, 589 patients were considered for the analysis and in 179 (30.4%) HbA1c was superior to 6.5%. The mean overall HbA1c level was 6.37 ± 1.27%. In insulin-dependent patients it was 8.14 ± 1.55%, and in cases under oral medication 7.24 ± 1.11%. In patients under diet control the mean HbA1c value was 6.72 ± 1.01 (Table 1).

TABLE 1
Distribution of the HbA1c among population

Preoperative HbA1c	All patients	Insulin dependent	Oral medication	Diet controlled	No diabetes
Total	589 (100%)	90 (15.28%)	81 (13.75%)	23 (3.9%)	395 (67.06%)
<=5	30 (100%)	1 (3.33%)	1 (3.33%)	0 (0%)	28 (93.33%)
>5 to <=6	270 (100%)	1 (0.37%)	7 (2.59%)	7 (2.59%)	255 (94.44%)
>6 to <=7	168 (100%)	23 (13.69%)	31 (18.45%)	9 (5.36%)	105 (62.5%)
>7 to <=8	59 (100%)	22 (37.29%)	26 (44.07%)	5 (8.47%)	6 (10.17%)
>8 to <=9	36 (100%)	22 (61.11%)	13 (36.11%)	1 (2.78%)	0 (0%)
>9	26 (100%)	21 (80.77%)	3 (11.54%)	1 (3.85%)	1 (3.85%)
Mean Hb1Ac ± SD	6.37 ± 1.27	8.14 ± 1.55	7.24 ± 1.11	6.72 ± 1.01	5.77 ± 0.55

The mean HbA1c in the group ≤ 6.5% was 5.72 ± 0.44% and in the group superior to 6.5% it was 7.86 ± 1.27%. Patient preoperative characteristics are presented in Table 2.

Patients in the HbA1c>6.5% group had a lower ejection fraction 50.8 ± 13.0 vs. 54.8 ± 10.8 (p<0.001), were younger 66.6 ± 9.1 vs. 68.7 ± 9.9 (p=0.01), have had more frequently three vessel diseases at 88.3% vs. 79.5% (p=0.012) and have had less frequent left main stenosis 19.0% vs. 30.0% (p=0.006). However, they have had a more frequent history of congestive heart failure 28.5% vs. 19.8% (p=0.020) and history of peripheral vascular disease 17.3% vs. 11.0% (p=0.036).

Stratifying the impact of the HbA1c >8% did not reveal any difference as compared to the HbA1c >6.5% and <8% (see supplemental Table 1) for crude descriptive statistics.

TABLE 2
Patient characteristics before and after IPTW

	Before IPTW				After IPTW			
	HbA1c ≤6.5, n = 410	HbA1c >6.5, n = 179	Diff.	p	HbA1c ≤6.5, n = 366	HbA1c >6.5, n = 157	Diff.	p
Age, y	68.7 ± 9.9	66.6 ± 9.1	-0.225	0.014	68.1 ± 9.8	67.7 ± 9.4	-0.038	0.688
Ejection fraction, %	54.8 ± 10.8	50.8 ± 13.0	-0.34	0	54.0 ± 11.1	54.5 ± 10.2	0.052	0.58
Female	63 (15.4)	20 (11.2)	0.014	0.18	50 (13.6)	23 (14.9)	-0.005	0.708
3 vessel CAD	326 (79.5)	158 (88.3)	-0.032	0.012	311 (85.1)	130 (82.8)	0.008	0.571
Main stem	123 (30.0)	34 (19.0)	0.048	0.006	91 (24.9)	38 (24.0)	0.004	0.845
Peripheral aretery disease	45 (11.0)	31 (17.3)	-0.022	0.036	46 (12.5)	25 (16.2)	-0.013	0.28
Preoperative Stroke	29 (7.1)	17 (9.5)	-0.007	0.315	28 (7.7)	16 (10.0)	-0.007	0.41
Renal disease	20 (4.9)	8 (4.5)	0.001	0.83	20 (5.5)	5 (3.1)	0.005	0.248

Dialysis	4 (1.0)	3 (1.7)	-0.001	0.476	4 (1.2)	1 (0.5)	0.001	0.435
COPD	38 (9.3)	21 (11.7)	-0.008	0.361	36 (9.7)	16 (10.4)	-0.002	0.82
Prior MI	222 (54.1)	99 (55.3)	-0.006	0.795	200 (54.7)	81 (51.4)	0.016	0.511
Hypertension	365 (89.0)	168 (93.9)	-0.014	0.07	329 (89.9)	147 (93.5)	-0.01	0.22
Hypercholesteremia	331 (80.7)	157 (87.7)	-0.026	0.04	309 (84.5)	135 (85.7)	-0.004	0.74
NYHA III or IV	81 (19.8)	51 (28.5)	-0.038	0.02	76 (20.8)	34 (21.5)	-0.003	0.847
AF preop	22 (5.4)	11 (6.1)	-0.002	0.705	20 (5.5)	10 (6.4)	-0.002	0.716
Current Smoker	102 (24.9)	60 (33.5)	-0.039	0.031	100 (27.4)	40 (25.4)	0.009	0.645
EuroSCORE >6	80 (19.5)	32 (17.9)	0.006	0.642	69 (18.9)	25 (15.6)	0.012	0.373
Diabetes melitus				0				0
- No	370 (90.2)	25 (14.0)	-1.214		329 (90.0)	21 (13.5)	-1.216	
- Diet	12 (2.9)	11 (6.1)	0.154		11 (2.9)	8 (5.2)	0.115	
- On Oral antidiabethics	20 (4.9)	61 (34.1)	0.692		18 (5.0)	53 (33.5)	0.681	
- Insulin	8 (2.0)	82 (45.8)	0.915		8 (2.1)	75 (47.8)	0.934	

COPD; Chronic obstructive pulmonary disease, NYHA: New York Heart Association; Functional Classification, MI: myocardial infarction, IPTW: inverse probability of treatment weighting

Using propensity modelling to construct IPTW, the mentioned differences were eliminated (Table 2), and the number of cases after IPTW decreased in HbA1c>6.5% to 157 and in HbA1c≤6.5% to 366 patients. The standardized differences of all pre-operative patient characteristics dropped below 0.06, indicating no meaningful difference, with the only exception of diabetes, which is causally related to HbA1c. The propensity distribution of the two groups is shown in Figure 1; the tails outside the red lines have been trimmed before the analysis.

Regarding the intraoperative variables that may influence outcome, such as cross clamp time, number of performed peripheral anastomosis, or usage of the bilateral internal mammary artery (BIMA), as well as complete arterial revascularization did not differ between the groups before and after IPTW (Table 3).

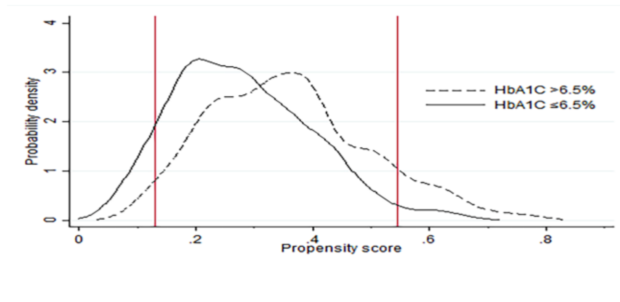

Figure 1) *Kernel density distribution of the propensity score in patients with preoperative HbA1c ≤ and >6.5%*

TABLE 3
Intraoperative characteristics

	Before IPTW				After IPTW			
	HbA1c ≤6.5, n = 410	**HbA1c >6.5, n = 179**	**Diff.**	**p**	**HbA1c ≤6.5, n = 366**	**HbA1c >6.5, n = 157**	**Diff.**	**p**
Number of distal anastomoses	3.5 ± 1.2	3.6 ± 1.0	0.084	0.361	3.5 ±1.2	3.5 ± 1.2	-0.033	0.728
Perfusion time, min	92.8 ± 35.7	94.0 ± 26.7	0.037	0.695	93.7 ± 35.0	91.3 ± 26.7	-0.076	0.4
Aortic clamping time, min	59.0 ± 24.2	59.5 ± 23.6	0.024	0.784	59.0 ± 24.1	58.9 ± 23.2	-0.007	0.945
LIMA	395 (96.3)	174 (97.2)	-0.002	0.595	352 (96.2)	153 (97.5)	-0.002	0.48
RIMA	65 (15.9)	34 (19.0)	-0.012	0.349	60 (16.5)	28 (17.8)	-0.005	0.712
BIMA	64 (15.6)	34 (19.0)	-0.013	0.311	59 (16.2)	28 (17.8)	-0.006	0.662
Arteria Radialis	123 (30.0)	45 (25.1)	0.022	0.23	112 (30.7)	39 (24.5)	0.028	0.177
Total arterial revascularisation	113 (27.6)	42 (23.5)	0.018	0.299	96 (26.1)	40 (25.2)	0.004	0.83
LIMA harvested skeletonized	232 (56.6)	104 (58.1)	-0.007	0.733	203 (55.3)	96 (61.1)	-0.029	0.244
RIMA harvested skeletonized	57 (13.9)	30 (16.8)	-0.01	0.369	52 (14.2)	26 (16.3)	-0.008	0.541
BIMA harvested skeletonized	49 (12.0)	25 (14.0)	-0.007	0.498	44 (11.9)	21 (13.2)	-0.004	0.695
OPCABG	65 (15.9)	24 (13.4)	0.009	0.446	54 (14.8)	25 (16.1)	-0.005	0.736

LIMA: Left Internal Mammary Artery; RIMA; Right Internal Mammary Artery; BIMA: Bilateral Internal Mammary Artery; OPCABG: Off Pump Aorto-Coronary Bypass Graft; IPTW: Inverse Probability of Treatment Weighting

Thirty-day mortality was higher in the HbA1c>6.5% cohort 3.4% vs. 1.0% in HbA1c≤6.5% (p=0.054), but did not reach statistical significance either before, or after IPTW (3.5% vs. 1.1%) p=0.076. This was similar for postinterventional myocardial infraction, which was higher in the HbA1c>6.5% cohort, but not statistically significant before (5.0% vs. 2.4%) p=0.109 or after IPTW (4.4% vs. 2.3%) p=0.229. Major adverse events such as stroke, sepsis, and renal failure with and without the need for renal replacement therapy, were significantly higher in HbA1c>6.5% before and after IPTW (Table 4).

TABLE 4
Postoperative data

	Before IPTW				After IPTW			
	HbA1C ≤6.5, n = 410	**Hb1AC>6.5, n = 179**	**Diff.**	**p**	**HbA1C ≤6.5, n = 366**	**Hb1AC>6.5, n = 157**	**Diff.**	**p**
30 day mortality	4 (1.0)	6 (3.4)	-0.003	0.054	4 (1.1)	6 (3.5)	-0.004	0.076
ICU stay >2 days	83 (20.2)	56 (31.3)	-0.049	0.004	69 (18.9)	44 (28.0)	-0.039	0.028
Myocardial infarction	10 (2.4)	9 (5.0)	-0.005	0.109	8 (2.3)	7 (4.4)	-0.004	0.229
Postoperativ Stroke	7 (1.7)	10 (5.6)	-0.007	0.014	6 (1.6)	9 (5.7)	-0.008	0.024
MACCE	16 (3.9)	21 (11.7)	-0.021	0.001	14 (3.9)	18 (11.5)	-0.02	0.003

Atrial fibrillation	95 (23.2)	41 (22.9)	0.001	0.944	79 (21.6)	36 (23.2)	-0.007	0.69
Permanent pacemaker	5 (1.2)	1 (0.6)	0.001	0.474	3 (0.8)	1 (0.9)	0	0.903
Wound infection	10 (2.4)	18 (10.1)	-0.019	0	7 (1.9)	16 (9.9)	-0.019	0
Sepsis	5 (1.2)	8 (4.5)	-0.005	0.021	4 (1.0)	8 (5.3)	-0.008	0.008
Sternal infection	8 (2.0)	16 (8.9)	-0.016	0	5 (1.3)	15 (9.4)	-0.019	0
Pulmonary infection	17 (4.1)	20 (11.2)	-0.019	0.002	16 (4.4)	18 (11.2)	-0.018	0.007
Infection	27 (6.6)	33 (18.4)	-0.04	0	24 (6.6)	27 (17.4)	-0.036	0
Postoperative renal failure	7 (1.7)	10 (5.6)	-0.007	0.014	7 (2.0)	9 (6.0)	-0.008	0.03
Renal substitution therapy	1 (0.2)	4 (2.2)	-0.002	0.046	1 (0.3)	4 (2.5)	-0.003	0.048
Intubation >72h	5 (1.2)	8 (4.5)	-0.005	0.021	4 (1.1)	7 (4.2)	-0.005	0.033
Reoperation for bleeding	11 (2.7)	0 (0.0)	0.003	0	10 (2.7)	0 (0.0)	0.003	0

ICU: Intensive Care Unit; MACCE: Major Cerebrovascular or Cardiovascular Event; IPTW: Inverse Probability of Treatment Weighting

Overall infection rate, sternal infection rate, wound infections and pulmonary infections requiring antibiotics therapy were higher in the HbA1c>6.5% group before and after IPTW (Table 4).

A prolonged intensive care unit stay of more than 48 hours before (20.2% vs. 31.3%, p=0.004), and after IPTW (18.9% vs. 28.0%, p=0.028) was higher in the HbA1c>6.5% cohort. The prevalence of prolonged intubation (>72 hours) was higher in patients having HbA1c>6.5% before (4.5% vs. 1.2%, p=0.021), as well after IPTW (4.2% vs. 1.1%, p=0.033). This was similar for re-exploration because of bleeding (2.7% vs. 0.0%, p<0.01 before and 2.7% vs. 0.0%, p<0.01 after IPTW) (Table 4). Diabetes was significantly associated with most of the relevant outcomes such as MACCE (OR 2.56, 95% CI 1.31 to 5, p=0.006), sternal infection (OR 3.59, 95% CI 1.54 to 8.37, p=0.003) and wound infection (OR 2.87, 95% CI 1.33 to 6.19, p=0.007). However, adding Hb1AC stratified by 6.5% to the model significantly improved the likelihood of the model (p=0.036, p=0.026 and p=0.007, respectively). On the other hand, adding diabetes to a model that included Hb1AC stratified by 6.5% did not improve the likelihood of the model (p=0.844, p=0.77 and p=0.784, respectively, supplemental Table 2).

Patients having HbA1c>6.5% had a higher risk for major cardiovascular event before and after IPTW (Table 5). This was similar for adverse events such as sternal infection, wound infection, pulmonary infection, and sepsis. The composite infection rate comprising pulmonary infection, sternal infection and wound infection was higher in the HbA1c>6.5% group, and the risk for renal failure and the risk for renal substitution therapy was also higher (Table 5).

TABLE 5
Association of pre-operative HbA1c>6.5% with postoperative complications

Variables	Before IPTW		After IPTW	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
MACCE	3.27 (1.66 to 6.44)	0.001	3.19 (1.48 to 6.87)	0.003
Sternal infection	4.93 (2.07 to 11.75)	0	8.07 (2.79 to 23.39)	0
Infection	3.21 (1.86 to 5.52)	0	2.99 (1.64 to 5.46)	0
Pulmonary infection	2.91 (1.48 to 5.70)	0.002	2.72 (1.31 to 5.68)	0.007
Sepsis	3.79 (1.22 to 11.75)	0.021	5.36 (1.56 to 18.46)	0.008
Wound infection	4.47 (2.02 to 9.90)	0	5.77 (2.26 to 14.75)	0
Postoperative renal failure	3.41 (1.28 to 9.10)	0.014	3.16 (1.12 to 8.88)	0.03
Renal substitution therapy	9.35 (1.04 to 84.24)	0.046	9.39 (1.02 to 86.48)	0.048

MACCE: Major Cerebrovascular or Cardiovascular Event; OR: Odds Ration; CI: Confidential Interval; IPTW: Inverse Probability of Treatment Weighting

Usage of BIMA per se did not have any significant influence on sternal wound infections (Odds ratio (OR) 1.58, 95% CI 0.6-4.18, p=0.34), however HbA1c>6.5% augmented significantly the risk for sternal infection (OR 4.85, CI 2.03-11.58, p<0.01), when adjusted for use of BIMA.

DISCUSSION

The main finding of our study is that sub-optimally-treated diabetes mellitus in the preoperative period is a predictive factor for adverse events following elective coronary bypass surgery, including events such as stroke, sternal infection, as well the incidence of acute renal failure.

HbA1c was chosen as a marker for adequate long-term glycaemia treatment. HbA1c is a result of an irreversible bond between hemoglobin and glucose, resulting in stable complex glycated hemoglobin unit. Since the life span of red blood cells is between 90 to 120 days, the glycated hemoglobin complex is not adjusted by short-term glycaemia alteration and as such gives us adequate insight into the blood glucose level over a 3- to 4-month period. It is recommended in patients with diabetes to target a HbA1c level inferior to 7%, which per se is associated with reduced complications allied to diabetes mellitus (12-14). In order to attempt to investigate the effectiveness of the preoperative diabetic treatment, we considered a threshold of HbA1c of 6.5% to differentiate between optimal vs. suboptimal diabetes control. The threshold of 6.5% demonstrates a specificity superior to 99% and may be considered as a diagnostic marker predicting adverse events following coronary bypass surgery (15-17). We stratified our cohort, independently of preoperatively diagnosed diabetes, into two groups, according to whether the HbA1c level was superior to 6.5% or ≤ 6.5%.

Major cardiovascular events defined as a combination of stroke, myocardial infarction and cardiac related mortality, were associated with preoperatively elevated HbA1c. Out of these three events, only the risk for stroke during the hospital stay in the group with HbA1c >6.5% was significantly higher. This was not the case for incidence of myocardial infarction, or rate of in-hospitality mortality. The in-hospital mortality was with 3.4% vs. 1.0% before (p=0.05) and with 3.5% vs. 1.1% (p=0.07) after IPTW higher in HbA1c>6.5% population, however did not reach the statistical significance. These findings were in contrast to the literature, where suboptimal treated diabetes detected with elevated HbA1c was associated with an increase in hospital mortality. However, this discrepancy may be in part explained by a simple fact, namely the HbA1c threshold in large multicentric reports, was set in part superior to 8.5% (18,19). Consequently, the elevated HbA1c population was in some instance sicker and as such carried within an elevated risk for the perioperative complications (18,19). In reports where the critical value of the HbA1c was set under 7.5%, in-hospital mortality was not higher (20,21). In our cohort the mean HbA1c in suboptimal treated group was barely superior to 7.5%, and probably as such the cohort may be considered as moderately exposed to the risk for perioperative mortality. This moderate risk is underlined by the fact that only 20% of patients in both groups were in elevated EuroSCORE range.

The most important observation in the selected cohort is in regard to the infection rate, which needs further detailed discussion. An HbA1c>6.5% is associated with an elevated infection rate, including wound infection, pulmonary infection, as well the incidence of sternal infection. In our cohort, despite the relatively low HbA1c threshold, the risk for wound infection was clearly associated to the elevated HbA1c. This finding is in line with the recent literature, where in a relatively large cohort it was confirmed that each unit elevation of HbA1c increases significantly the risk for wound infections (18).

At this point, we have to mention that the reports focusing on impact of the HbA1c following coronary revascularization (15-20) are not evaluating the concomitant effect of BIMA usage on incidence of wound infection in this particular population. In our cohort, complete arterial revascularization was performed in around 30% of cohort, and BIMA usage was at 14% (Table 3). However, the usage of BIMA per se was not associated with elevated incidence of sternal infections, instead, HbA1c>6.5% augmented significantly the risk for sternal infection (OR 4.85, CI 2.03-11.58, p<0.01), when adjusted for use of BIMA. It seems that suboptimal diabetes treatment is one of the striking risk factors for sternal infection following elective coronary revascularization. The usage of BIMA in diabetic patients as such is not predictive for sternal infections, however a consequent treatment of diabetes mellitus, targeting HbA1c inferior to 6.5% is crucial to avoid this devastating complication. The relationship of elevated HbA1c and adverse events, such as incidence of new renal failure, prolonged ICU stay, as well prolonged intubation was in line with previously published reports (15-20).

In this single-center study we aimed to evaluate the correlation between adverse events following coronary revascularization and HbA1c as a marker indicating long-term glycemia state. The reference level was set to a relatively low range to especially obtain insight into how moderate HbA1c levels influence outcome. As such, we addressed glycemia levels independently of the diabetes treatment modality. However, one has to be aware that the recent literature on the perioperative management of glycemia is in some manner controversial. Reports exist where independently from perioperative glucose level; the short-term outcome following coronary bypass revascularization does not reflect any difference (22).

The main limitation of this study is that it has been conducted in a single center and use of propensity techniques to calculate the impact of increased HbA1c on short-term outcome can only reduce confounding by cardiovascular risk factors. Secondly, although long-term results may be important, in order to evaluate effect of the diabetes mellitus treatment, we believe that the method chosen a marker with a short-term life spam and is also influenced by medical treatment may not be an ideal subject for long term follow up. This especially if diabetes treatment evaluated during the follow up to be suboptimal would change in its modality, may substantially influence the data evaluation.

CONCLUSION

In conclusion, we found that HbA1c>6.5% in combination with BIMA leads to an elevated risk for sternal infections. Further, HbA1c>6.5% as such, is associated with adverse events such a stroke and new renal failure post coronary bypass surgery. However, HbA1c>6.5% does not have any impact on mortality from myocardial infarction or incidence of new onset of postoperative atrial fibrillation.

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