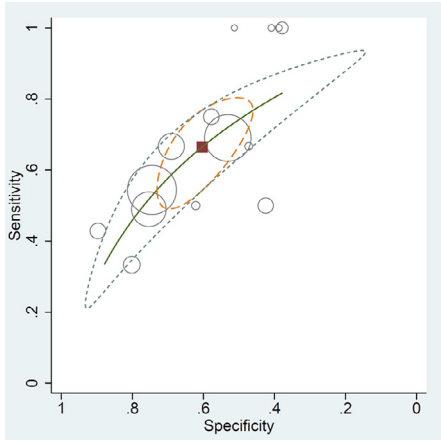
Glycated Hemoglobin and the Risk of Sternal Wound Infection After Adult Cardiac Surgery: A Systematic Review and Meta-Analysis

Fausto Biancari, MD, PhD,[*,†] *and Salvatore Giordano, MD, PhD*[‡,§]

Increased glycated hemoglobin (HbA1c) has been shown to increase the risk of mortality, myocardial infarction, and stroke after cardiac surgery, whereas its impact on the development of sternal wound infection (SWI) is less clear. A systematic review and meta-analysis were performed to evaluate the impact of preoperative HbA1c levels on the occurrence of SWI after adult cardiac surgery. Fourteen studies including 17,609 patients fulfilled the inclusion criteria and were included in this analysis. Diagnostic test meta-analysis of studies evaluating baseline HbA1c cut-off values ranging from 6% to 7% DCCT units (42–53 mmol/mol IFCC units) showed that the diagnostic odds ratio for deep SWI was 3.02 (95% confidence interval [CI] 2.10–4.35), while the diagnostic odds ratio for any SWI was 2.81 (95% CI 2.02–3.93). Binary meta-analysis confirmed that baseline HbA1c cut-off values ranging from 6% to 7% increased the risk for deep SWI (pooled incidence 2.7% vs 0.8%, risk ratio [RR] 3.01, 95% CI 2.32–3.90, I^2 0%). Six studies included only diabetics and their pooled RR for deep SWI was 2.94 (1.59–5.45, I^2 0%). Nine studies evaluated an HbA1c cut-off value of 7% and their RR for deep SWI was 3.22 (95% CI 2.38–4.37, I^2 0%). The RR for any SWI was 2.92 (95% CI 2.42–3.53, I^2 0%). This pooled analysis showed that the risk of SWI is substantially increased when preoperative HbA1c levels are over 6–7%. Future studies should evaluate whether postponing surgery for optimization of the glycemic control can reduce the risk of SWI in patients with increased levels of HbA1c.

Semin Thoracic Surg 31:465–467

Keywords: Glycated hemoglobin, Glycosylated hemoglobin, HbA1c, Sternal wound infection, Cardiac surgery, Coronary artery bypass grafting



HbA1c and risk of deep sternal wound infection after adult cardiac surgery.

Central Message

Elevated glycated hemoglobin (HbA1c) is associated with increased risk of sternal wound infection and should be routinely measured before cardiac surgery, at least in patients with known diabetes.

Glycated hemoglobin (HbA1c) is the end-product of nonenzymatic glycosylation of hemoglobin and its increased level is a marker of poor glycemic control.[1] Advanced glycation end-products are responsible for impairment of immunity,[1] which in turn significantly increases the infection risk in diabetics.[2] Increased HbA1c has also been shown to increase the risk of mortality, myocardial infarction, and stroke after cardiac surgery,[3] whereas its impact on the occurrence of sternal wound infection (SWI) is less clear. This issue has been investigated in the present meta-analysis.

MATERIAL AND METHODS

The protocol of this study was registered in the PROSPERO registry (CRD42018090160). PubMed, Scopus, and Google Scholar were searched on August 20, 2018, without date and language restriction. Search criteria included the following terms: "HbA1c," "glycated hemoglobin," "glycosylated hemoglobin," "hemoglobin A1c," "wound," and "surgical site infection." Reference lists of pertinent articles were also reviewed. Observational studies evaluating the impact of preoperative

*Heart Center, Turku University Hospital and Department of Surgery, University of Turku, Turku, Finland
†Department of Surgery, University of Oulu, Oulu, Finland
‡Department of Surgery, Satakunta Central Hospital, Pori, Finland
§Department of Plastic and General Surgery, Turku University Hospital and University of Turku, Turku, Finland

Funding: This study was not financially supported.

Conflicts of Interest: The authors do not have any conflict of interest related to this study.

Address reprint requests to Fausto Biancari, MD, PhD, Heart Center, Turku University Hospital, Hämeentie 11, PL 52, Turku 20521, Finland. E-mail: faustobiancari@yahoo.it

HbA1c levels on the occurrence of SWI after any adult cardiac surgery procedure were considered for this analysis. Population, Intervention, Comparator, Outcomes, and Study design (PICOS) of this analysis and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist are summarized in Supplementary Tables 1 and 2. Abstracts and full-text articles were independently reviewed and data collected by 2 investigators (F.B., S.G.). Discrepancies were resolved through consensus. The QUADAS-2 risk of bias tool[4] was used to assess the methodological quality of the included studies. The exposure of interest was increased preoperative levels of HbA1c as reported in the included studies. The primary outcome was deep SWI/mediastinitis and secondary outcome was any superficial or deep SWI. The definition criteria of SWI were expected to vary between studies and were kept as originally defined in the retrieved articles.

Statistical analysis was performed using STATA v. 15.1 statistical software (StataCorp, College Station, TX). Outcomes are reported as pooled proportions with 95% confidence intervals (CIs). Since the included studies evaluated the accuracy of preoperative HbA1c to predict postoperative SWI using different cut-off values, diagnostic test meta-analysis was performed to estimate the diagnostic odds ratio (DOR). Furthermore, the outcomes of two-arm analyses employing HbA1c ranging from 6% to 7% were pooled with the random-effects method leading to computations of risk ratios (RR) with 95% CI. Sensitivity analysis for different HbA1c cut-off values, elective procedures, and in diabetics was performed. I^2 statistic was used to estimate the heterogeneity of the studies, with $I^2 > 40\%$ as a threshold for significant heterogeneity. Publication bias was assessed by inspecting funnel plot asymmetry. $P < 0.05$ was set for statistical significance.

RESULTS

Of the 311 records identified, 14 studies fulfilled the inclusion criteria and were included in this analysis (Supplementary Fig. 1). Their characteristics are summarized in Table 1 and Supplementary Figure 2. Diagnostic test meta-analysis including studies evaluating baseline HbA1c cut-off values ranging from 6% to 7% DCCT units (42−53 mmol/mol IFCC units) showed that the DOR for deep SWI was 3.02 (95% CI 2.10−4.35), with a sensitivity of 66.5% and a specificity of 60.3% (Fig. 1). The DOR for any SWI was 2.81 (95% CI 2.02−3.93), with a sensitivity of 64.7% and a specificity of 60.6%.

Binary meta-analysis confirmed that baseline HbA1c cut-off values ranging from 6% to 7% increased the risk for deep SWI (pooled incidence 2.7% vs 0.8%, RR 3.01, 95% CI 2.32−3.90, I^2 0%; Fig. 1, Supplementary Fig. 3). Six studies included only diabetics and their pooled RR for deep SWI was 2.94 (1.59−5.45, I^2 0%). Nine studies evaluated a HbA1c cut-off value of 7% and their RR for deep SWI was 3.22 (95% CI 2.38−4.37, I^2 0%). The RR for any SWI was 2.92 (95% CI 2.42−3.53, I^2 0%). Two studies[4,5] reported on adjusted estimated of continuous HbA1c levels for deep

Table 1. Characteristics and Data of the Included Studies

Author	Year	Country	Study Design	Study Period	No. of Patients	CABG (%)	Diabetics (%)	Postop Glycemic Control	HbA1c Cutoff
Alserius	2008	Sweden	P	2002−2004	605	100	100	NS	≥7%
Finger	2017	USA	R	2014	531	100	34	In ICU range 5.5−7.9 mmol/L, in ward NS	>7%
Fohl	2013	USA	R	2005−2009	616	100	100	Range 5.3−7.8 mmol/L	≥7%
Gumus	2013	Turkey	R	2010−2012	510	74	40	Range 6.7−7.8 mmol/L	≥6%
Göksedef	2010	Turkey	P	2007−2008	150	100	NS	NS	>7%
Halkos	2008	USA	R	2002−2007	5199	100	34	In ICU range 4.4−6.3 mmol/L, in ward <8.3 mmol/L	≥7%
Narayan	2017	India	R	2011−2014	4678	51	NS	<8.3 mmol/L	≥6.5%
Nicolini	2018	Europe	P	2015−2016	2606	92	36	NS	≥7%
Ramadan	2018	Egypt	P	2013−2015	80	100	100	<8.3 mmol/L	>7%
Santos	2015	Argentina	P	NS	96	100	100	In ICU <6.7 mmol/L, in ward <8.3 mmol/L	>7%
Sato	2010	Canada	P	2008−2009	130	60	100	Range 4.0−8.0 mmol/L	≥6.5%
Subramaniam	2014	USA	P	2008−2011	1461	100	38	Range 5.0−6.7 mmol/L	≥6.5%
Tarazi	2017	Egypt	R	2014−2016	101	100	NS	NS	>7%
Tsuruta	2011	Japan	P	2002−2007	306	100	100	NS	≥6.5%

NS, not stated; P, prospective study; R, retrospective study.

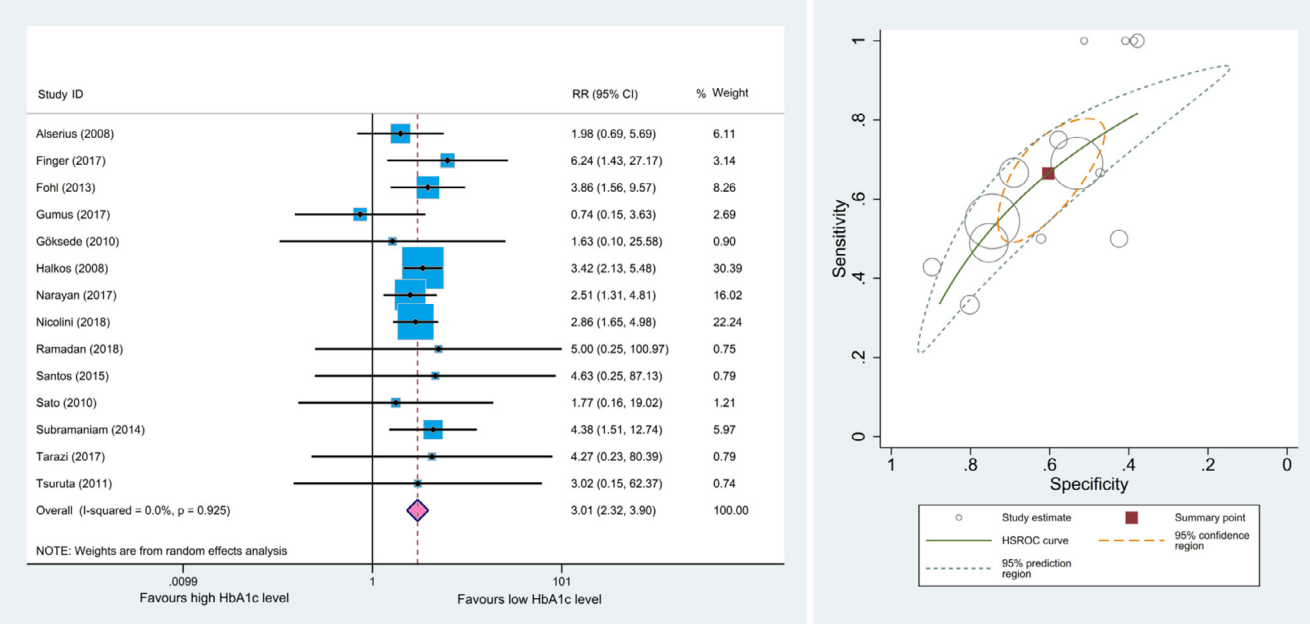


Figure 1. Forest plot and hierarchical summary receiver operating characteristic plot of the impact of baseline glycated hemoglobin (HbA1c) ranging from 6% to 7% on the occurrence of deep sternal wound infection after adult cardiac surgery. CI, confidence interval; HSROC, hierarchical summary receiver operating characteristic; ID, identification; RR, risk ratio.

SWI and their pooled RR was 1.33 (95% CI 1.19–1.46, I^2 0%).

DISCUSSION

Diabetes is a risk factor for surgical site infection[5] and this pooled analysis showed that such a risk is substantially increased when glycemia is poorly controlled as shown by HbA1c levels over 6–7%. These findings are clinically relevant because HbA1c may allow a stratification of the risk of SWI and may guide preventative strategies to reduce the risk of such a severe complication. However, the included studies might be affected by significant clinical heterogeneity in the use and harvesting technique of internal mammary arteries, antibiotic prophylaxis, and wound care. Future studies should evaluate whether postponing surgery for optimization of the glycemic control can reduce the risk of SWI in patients with increased levels of HbA1c.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version at doi: 10.1053/j.semtcvs.2019.02.029.

REFERENCES

1. Iannantuoni F, Diaz-Morales N, Escribano-Lopez I, et al: Does glycemic control modulate the impairment of NLRP3 inflammasome activation in type 2 diabetes? Antioxid Redox Signal 2018. (in press)
2. Mor A, Dekkers O, Nielsen J, et al: Impact of glycemic control on risk of infections in patients with type 2 diabetes: A population-based cohort study. Am J Epidemiol 186:227–236, 2017
3. Zheng J, Cheng J, Wang T, et al: Does HbA1c level have clinical implications in diabetic patients undergoing coronary artery bypass grafting? A systematic review and meta-analysis. Int J Endocrinol 2017:1537213, 2017
4. Whiting P, Rutjes A, Westwood M, et al: QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155:529–536, 2011
5. Martin E, Kaye K, Knott C, et al: Diabetes and risk of surgical site infection: A systematic review and meta-analysis. Infect Control Hosp Epidemiol 37:88–99, 2016