Interactive CardioVascular and Thoracic Surgery 17 (2013) 1000–1008
doi:10.1093/icvts/ivt351 Advance Access publication 10 September 2013

Is there a role for HbA1c in predicting mortality and morbidity outcomes after coronary artery bypass graft surgery?

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Received 20 March 2013; received in revised form 9 July 2013; accepted 17 July 2013

Abstract

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was is there a role for HbA1c in predicting morbidity and mortality outcomes after coronary artery bypass surgery? Eleven studies presented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. The studies presented analyse the relationship between preoperative HbA1c levels and postoperative outcomes following coronary artery bypass graft (CABG) in diabetic, non-diabetic or mixed patient groups. Four studies found significant increases in early and late mortality at higher HbA1c levels, regardless of a preoperative diagnosis of diabetes. One study demonstrated that 30-day survival outcomes were significantly worse in patients with previously undiagnosed diabetes and elevated HbA1c compared with those with good control [HbA1c >6%; odds ratio 1.53, confidence interval (CI) (1.24–1.91); $P = 0.0005$]. However, four studies of early mortality outcomes in diabetic patients only showed no significant differences between patients with normal and those with deranged HbA1c levels ($P = 0.99$). There were mixed reports on morbidity outcomes. Three studies identified a significant increase in infectious complications in patients with poorly controlled HbA1c, two of which were irrespective of previous diabetic status [deep sternal wound infection ($P = 0.014$); superficial sternal wound infection ($P = 0.007$) and minor infections ($P = 0.006$) in poorly controlled diabetics only]. Four studies presented outcomes for total length of stay (LOS). Three of these papers looked specifically at diabetic patients, of which two found no significant differences in length of stay between good and poor preoperative glycaemic control [LOS: $P = 0.59$ and 0.86 vs $P < 0.001$]. However, elevated HbA1c vs normal HbA1c was associated with prolonged stay in hospital and in intensive care unit (ICU) in patients irrespective of previous diabetic status [total LOS ($P < 0.001$)]. Elevated HbA1c levels were also a significant predictor of reduced intraoperative insulin sensitivity in diabetic patients ($R = -0.527$; $P < 0.001$). Furthermore, higher HbA1c levels were associated with a reduced incidence of postoperative atrial fibrillation ($P = 0.001$). We conclude that elevated HbA1c is a strong predictor of mortality and morbidity irrespective of previous diabetic status. In particular, the mortality risk for CABG is quadrupled at HbA1c levels >8.6%. Some studies have called into question the predictive value of HbA1c on short-term outcomes in well-controlled diabetics; however, long-term outcomes in this population have not been reported.

Keywords: Glycosylated haemoglobin • Coronary artery bypass graft • Myocardial infarct • Deep sternal wound infection • Superficial sternal wound infection • Cerebrovascular accident • World Health Organization

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the *ICVTS* [1].

THREE-PART QUESTION

In [patients undergoing CABG] is [HbA1c] a good predictor [of postoperative outcomes]?

CLINICAL SCENARIO

A patient in your clinic is due to have an isolated, elective coronary artery bypass graft (CABG) in 3 days. Their laboratory reports indicate they have poor glycaemic control (HbA1c > 7%). Discuss with the patient the implications of this result.

SEARCH STRATEGY

Medline 1950 to February 2012 using OVID interface [glycosylated haemoglobin OR HbA1c] AND [CABG OR cardiac surgery]

SEARCH OUTCOME

Forty-six papers were found using the reported search. From these, 11 papers were identified that provided the best evidence to answer the question. These are presented in Table 1.

RESULTS

Halkos *et al.* [2] conducted a prospective cohort study in 3089 diabetic and non-diabetic patients. HbA1c proved to be a powerful predictor of in-hospital mortality and morbidity postoperatively.

Significant increases in mortality ($P = 0.019$) and deep sternal wound infection (DSWI) ($P = 0.014$) were identified per unit increase in HbA1c. Elevated HbA1c ≥8.6% caused a four-fold increase in mortality. Postoperative complications such as renal failure (RF) [threshold 6.7, odds ratio (OR) 2.1], cerebrovascular accident (CVA) (threshold 7.8, OR 5.29) and DSWI (threshold 7.8, OR 5.29) occurred more frequently at HbA1c ≥ 8.6%. Complication rates were significantly higher in poor control HbA1c ≥7% vs good control <7% [RF, composite infection, DSWI, length of stay (LOS) ($P < 0.001$) and CVA ($P = 0.005$)].

Lower levels of HbA1c caused a significant increase in the incidence of atrial fibrillation (AF) whereas higher levels were protective [OR 0.89 (95% CI 0.80–0.98; $P = 0.014$)].

Halkos *et al.* [3] also investigated long-term outcomes. Their results show a significant reduction in long-term survival (OR 1.15, $P < 0.001$) per unit increase in HbA1c ≥7%.

Kinoshita *et al*. [4] investigated the association between HbA1c levels and the development of postoperative atrial fibrillation. Interestingly, HbA1c values were significantly lower in patients who developed AF postoperatively [HbA1c 5.8 (5.4–6.3) vs HbA1c 6.1 (5.5–7.2), $P = 0.01$]. Patients in the lowest HbA1c tertile showed the greatest incidence of postoperative AF (23.3 vs 17.4 and 12.5% for middle and upper tertiles, respectively). This trend was significant ($P = 0.01$).

Göksedef *et al*. [5] conducted a prospective study in 150 patients including diabetics and non-diabetics. The incidence of postoperative mediastinitis and local sternal infection ($P = 0.8$) had no significant association with HbA1c levels >7%. Furthermore, 30-day mortality outcomes were similar for both well and poorly controlled HbA1c groups (4.3% in HbA1c <7% vs 3.5% in HbA1c >7%, $P = 0.811$).

Sato *et al*. [6] conducted a prospective study in 273 patients. In contrast to the other studies, the presented cut-off for pathological and non-pathological HbA1c in this analysis is 6.5%.

A negative correlation between preoperative HbA1c levels and intraoperative insulin sensitivity was found in diabetic patients [$r = -0.527$; ($P < 0.001$)]. In comparison with non-diabetic patients, diabetic patients with HbA1c >6.5% showed a significant increase in the incidence of postoperative complications ($P = 0.010$). Additionally, they had more minor infections ($P = 0.006$) and a more labour-intensive stay in hospital [blood product usage (0.027); ICU LOS ($P = 0.030$); hospital LOS ($P < 0.001$)].

Matsuura *et al*. [7] performed a retrospective review in 101 diabetic patients. Postoperative outcomes were compared between patients with preoperative HbA1c (>6.5%) and those with good control (HbA1c <6.5%).

No significant differences were found in either group regarding early and late postoperative mortality ($P = 0.99$) and wound dehiscence (4.3% HbA1c <6.5 vs 9.3%; $P = 0.44$). Furthermore, differences in anastomoses number (2.76 ± 1.00 for HbA1c <6.5% vs 2.63 ± 0.80; $P = 0.45$), bilateral internal thoracic arteries usage (HbA1c <6.5% = 78.7 vs 81.4%; $P = 0.80$) and patency rates (HbA1c <6.5% = 96.9 for vs 99.2%; $P = 0.37$) in HbA1c <6.5 vs >6.5% were not significantly different.

Hudson *et al*. [8] performed a retrospective study in 1474 non-diabetic patients. Thirty-day mortality outcomes in patients with elevated HbA1c >6% were significantly higher than in those with HbA1c <6% [OR 1.53, CI (1.24–1.91), $P = 0.0005$ per unit increase in HbA1c]. This relationship continued after the exclusion of borderline diabetics. Patients with elevated baseline HbA1c values had a significant increase in the development of acute kidney injury postoperatively (OR 1.148, 95% CI 1.003–1.313, $P = 0.04$) (adjusted for known renal risk factors). Infection rates were not significantly associated with elevated HbA1c ($P = 0.48$).

Knapik *et al*. [9] conducted a retrospective review in 782 diabetic patients.

For comparison of outcomes, patients were matched to achieve similar preoperative status with a use of a Greedy matching procedure. For matched patients elevated HbA1c levels >7% were significantly associated with increased incidence of perioperative myocardial infarct (MI) compared with the HbA1c <7% group [4.7% HbA1c >7%, (±95% CI ± 3.18%) vs 0.6% HbA1c ≤7% (±95% CI ± 1.15%); $P = 0.01$] (matched preoperative variables). There were no significant differences in all other morbidity, early mortality and total LOS ($P = 0.59$) including ICU ($P = 0.94$) in either HbA1c group.

Tsuruta *et al*. [10] published a prospective study involving 893 diabetic patients. The patients were categorized into three groups depending on HbA1c level. There were no significant differences in all-cause ($P = 0.26$) or cardiac mortality ($P = 0.17$) (indicated by Kaplan–Meier's survival). There was an increased frequency of complications in the poorly controlled group (HbA1c ≥ 7.5%); however, the difference was non-significant.

Alserius *et al*. [11] conducted a prospective study correlating HbA1c concentrations with infection rate and mortality outcomes in 605 patients. Rates of superficial sternal wound infection were significantly increased in patients with HbA1c ≥6% (13.9% HbA1c ≥6% vs 5.2% when HbA1c <6%, $P = 0.007$). There was a trend towards higher rates of mediastinitis in HbA1c ≥6%; however, these results were not significant [4.9% in patients with HbA1c ≥6% vs 2.1% in HbA1c <6%, hazard ratio (HR) 1.9, (95% CI: 0.6–5.9) ($P = 0.20$)]. Mortality after 3 years was significantly higher in patients with HbA1c ≥6% after multivariable adjustment (all-cause mortality: 18.9% in HbA1c ≥6% vs 4.1% in HbA1c <6%, HR 5.4 (95% CI: 3–10) ($P < 0.001$).

McGinn *et al*. [12] conducted a retrospective study in 1045 patients. Elevated HbA1c levels irrespective of previous diabetic history are significantly associated with severe coronary artery disease [HbA1c ≥6%: mean 3.6 vs non-diabetic (<5.7%)/prediabetes (5.7–6.4%): mean 3.1; $P = 0.009$].

CLINICAL BOTTOM LINE

In 2011, the World Health Organization advocated the use of HbA1c in diagnosing diabetes. Previously, patients with no known diabetic history and poorly controlled HbA1c levels were placed into the non-diabetic category. These patients are potentially at higher risk of developing postoperative complications compared with known diabetics with good preoperative glycaemic control.

Elevated HbA1c is a strong predictor of mortality and morbidity irrespective of previous diabetic status. In particular, the mortality risk for CABG is quadrupled at HbA1c levels >8.6%. In elective situations, it has been proposed that these patients should be delayed for surgery until adequate glycaemic control is achieved.

Recently, a small number of studies have called into question the predictive value of HbA1c on short-term outcomes in well-controlled diabetes. Long-term outcomes in this population however have not been reported.

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Halkos *et al*. (2008), J Thorac Cardiovasc Surg, USA [2] Prospective cohort (level 2b)	Single academic centre Sample size: - 3089 patients undergoing primary, elective CABG - 2275/3089 (73.6%) HbA1c <7% - 814/3089 (26.4%) HbA1c ≥7% Diabetic group: - 1240/3089 (40%) patients had a history of diabetes - 516/1240 (42%) poorly controlled (HbA1c ≥7%) Non-diabetic group: - 1849/3089 (60%) patients no history of diabetes - 90/1849 (4.9%) had poorly controlled HbA1c ≥7% Features: - HbA1c measured preoperatively - 70% underwent off-pump CABG - All patients received uniform perioperative IV insulin regime - Data input into database prospectively	In-hospital mortality: - All patients Mortality: - Per unit increase in HbA1c - HbA1c level ≥8.6% Morbidity: - Per unit increase in HbA1c: - MI - DSWI - AF HbA1c level ≥7.0% vs HbA1c <7% - RF - Composite infection - DSWI - LOS - CVA HbA1c ≥8.6%: adjusted receiver operating characteristic value thresholds	1% (31/3089) OR 1.40 (95% CI: 1.06–1.86), *P* = 0.019 Associated with a four-fold increase in mortality (OR 4.4) - OR 1.55 (95% CI: 1.00–2.41), *P* = 0.05 - OR 1.38 (95% CI: 1.03–1.84), *P* = 0.029 - OR 0.89 (95% CI: 0.80–0.98), *P* = 0.014 reduced incidence of AF per unit increase in HbA1c - 1.8 vs 4.9% for HbA1c ≥7% - 0.9 vs 3.2% for HbA1c ≥7 - 0.4 vs 2.3% for HbA1c ≥7% - 5.9 vs 6.88 for HbA1c ≥7% (total *P* <0.001) - 1.3 vs 2.8% for HbA1c ≥7% (*P* = 0.005) - Renal failure (threshold 6.7, OR 2.1) - CVA (threshold 7.6, OR 2.23) - DSWI (threshold 7.8, OR 5.29) (All significant)	HbA1c is a powerful predictor of mortality and morbidity in the in-hospital setting after CABG Limitations: (i) The influence of pre-surgical HbA1c optimization regimes on postoperative outcomes were not compared (ii) During the retrospective analysis patients with no known diabetic history were classified as non-diabetic even if they were diagnosed with diabetes postoperatively
Halkos *et al*. (2008), Ann Thorac Surg, USA [3] Retrospective observational study (level 3b)	Single-academic centre Sample size: - 3201 patients undergoing primary, elective CABG - 2360 HbA1c <7% - 841 HbA1c ≥7% Diabetic group: - Diabetes well controlled (HbA1c <7%)—42%, 538/1285	Long-term unadjusted 5-year survival: - Poor control (HbA1c ≥7%) vs good control (HbA1c <7%) - Diabetics vs non-diabetics Diabetic survival outcomes based on treatment regime: - Insulin vs diet/oral hypoglycaemics	HbA1c ≥7% (82.3%) vs HbA1c <7% (87.6%), *P* = 0.001 Those with diabetes had reduced 5-year survival, *P* <0.001 Diabetics on insulin therapy 78.3 vs 82.4% Significantly worse 5-year survival outcomes, *P* = 0.006	Elevated HbA1c are significantly associated with reduced long-term survival following CABG surgery The authors propose that preoperative optimization of HbA1c may improve long-term survival HbA1c may also be used as a marker to provide reliable and accurate risk stratification to predict long-term morbidity in diabetic patients Limitations: (i) 70% of patients underwent off-pump CABG which is not reflective of national practice patterns for coronary revascularization

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Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
	- Non-diabetic group: No diabetes diagnosis and elevated preoperative HbA1c ≥7%: 4.9% (94/1916). (The undiagnosed and untreated diabetic group) - All patients received uniform perioperative IV insulin regime Mean follow-up: - 2.81 ± 1.40 years	Long-term survival per unit increase in HbA1c levels ≥7%: % reduction in 5 year survival	Lower long-term survival for each unit increase in HbA1c (OR 1.15), P <0.001 15% reduction in 5-year survival per unit increase in HbA1c Diabetes diagnosis preoperatively is not significantly associated with reduced long-term survival following CABG, P = 0.41 Patients with HbA1c ≥7% had a significantly higher presence of preoperative comorbidities	(ii) The authors do not provide information on glucose control/ treatment altercations/changes in morbidity status following discharge from hospital (iii) Retrospective review - patients who were defined as non-diabetic preoperatively with elevated HbA1c may have been diagnosed with diabetes in postoperative period
Kinoshita *et al*. (2012), Eur J Cardiothorac Surg, Japan [4] Retrospective study (level 3b)	Single centre Sample size: 805 patients analysed for postoperative AF following isolated off-pump CABG (Emergency cases, chronic AF and pacemaker rhythm excluded) Subdivision: - Analysis based on HbA1c levels categorized into tertiles - Analysis of 1% increments in HbA1c levels is also included - 283 patients with HbA1c between 3.8 and 5.6% - 282 patients with HbA1c between 5.7 and 6.7% - 240 patients with between HbA1c–6.8–11.4% Mixed study: - Diabetic and non-diabetic	Association between preoperative HbA1c and AF Median HbA1c value and associated AF Incidence of AF HbA1c as a predictor of postoperative AF	AF occurred in 159 (19.8%) of patients after surgery HbA1c 5.8 (5.4–6.3) vs HbA1c 6.1 (5.5–7.2), P = 0.01 Median value of HbA1c was significantly lower in patients who developed postoperative AF Lowest HbA1c tertile—80/ 283 (28.3%) had greatest incidence of AF postoperatively 0.70 (0.65–0.75), P = 0.01	Preoperative HbA1c is an independent predictor of AF occurrence following isolated, off-pump CABG Higher HbA1c levels are independently associated with a lower risk of AF occurrence in the postoperative period Limitations: (i) All patients were Japanese and were operated off-pump at a single centre (ii) Catecholamine dosages used during surgery were not recorded (iii) The incidence of AF may be underesti-mated as electro-cardiographic (ECG) telemetry was susceptible to motion artefact (iv) ECG monitoring was stopped after the eighth postoperative day
Göksedef *et al*. (2010), Turk J Thoracic Cardiovasc Surg, Turkey [5] Prospective study (level 2b)	Single-centre experience Sample size: - 150 patients underwent on-pump CABG - 53 (35.3%) diabetic - 97 non-diabetics Divided into 2 groups: HbA1c >7%	30-day mortality: HbA1c >7% HbA1c <7% Morbidity: Incidence of peripheral vascular disease All infections: - Local infection - Non-sternal infection	Similar for both groups: 4.3% in HbA1c <7% vs 3.5% in HbA1c >7%, P = 0.811 PVD: 26.3% in HbA1c >7 vs 12.9% in HbA1c <7%, P = 0.03 No significant difference in HbA1c <7% vs >7%, total	Elevated HbA1c levels do not significantly affect short-term infectious complications Patients with HbA1c >7% have a significantly higher incidence of PVD Limitations: (i) No long-term follow-up data for morbidity/mortality assessment (ii) Single-centre experience

Continued

Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
	HbA1c <7%	- DSWI	$P = 0.8$	
	Elevated HbA1c levels (>7%): - 35 (66%) diabetics - 22 (22.6%) non-diabetics	Elevated HbA1c levels vs elevated perio-perative glucose levels in: - Mediastinitis incidence	0% in elevated HbA1c vs 3% for raised perioperative glucose levels, $P = 0.01$	
	Patient demographic: - 106 males, 44 females - Mean age: 61.69 ± 10.06 years	- Local sternal infection incidence:	2.3% raised HbA1c vs 12.1% in raised perioperative glucose, $P = 0.002$	
	Features: All patients were managed according to the Portland protocol in perioperative period	Elevated perioperative glucose levels: - All infections	Glucose <126 mg/dl 4.7% vs 16.1% glucose >126 mg/dl, $P = 0.005$	
Sato *et al*. (2010), J Endocrinol Metab, USA [6] Prospective cohort (level 2b)	Single centre Sample size: - 273 patients - 143 non-diabetic - 130 diabetic Of the diabetic patients: - Group A: good control HbA1c <6.5% - Group B: poor control HbA1c >6.5% Patient demographics: - Similarly matched for both groups except: HbA1c and FBG, P <0.001 - Includes on-pump, elective CABG, valve and CABG and valve [Patients classified as non-diabetic prior to surgery but presenting with HbA1c >6% or Boehringer Mannheim (BM) >7 mmol/l were excluded] Intervention: Hyperinsulinemic-normoglycaemic clamp technique	Primary outcome: - Insulin sensitivity (Results for diabetics with poor preoperative control [HbA1c >6.5] are compared with diabetics with HbA1c <6.5% and non-diabetics) Secondary outcomes: - Results are for patients with HbA1c levels >6.5% vs non-diabetic patients (i) Major complications (ii) Severe infections - Minor infections: (a) Superficial wound infections (iii) Blood product usage (iv) LOS on ICU (v) LOS in hospital Incidence of major complications per 1 mg/kg^{-1}/min^{-1} reduction in insulin sensitivity	Correlation between HbA1c and intraoperative insulin sensitivity before termination of cardiopulmonary bypass (CPB): $R = -0.527$, P <0.001 (weak but significant correlation) $P = 0.010$ $P = 0.035$ $P = 0.006$ P =<0.05 Packed red cells ($P = 0.046$), Fresh frozen plasma (FFP) ($P = 0.035$), platelets (P <0.001) $P = 0.030$ P <0.001 Incidence of major complications increased significantly per unit reduction in insulin sensitivity, $P = 0.004$	HbA1c levels in diabetic patients can predict insulin sensitivity and potentially outcomes such as major complications following cardiac surgery Insulin resistance during surgery is associated with an increased risk of postoperative complications independent of the patients diabetic status Limitations: (i) Only patients who had a confirmed diagnosis of diabetes or who were on treatment were considered to be diabetic. Those labelled non-diabetic with HbA1c >6% were not eligible. The possibility that some non-diabetics may have had DM cannot be excluded
Matsura *et al*. (2009), Ann Thorac Surg, Japan [7] Retrospective review (level 3b)	Single centre Sample size: - 101 diabetic patients underwent off-pump, isolated, elective CABG HbA1c levels definition: - Group A: HbA1c <6.5% well controlled,	Number of anastomoses % use of bilateral internal thoracic arteries Graft patency rate	Group A: 2.76 ± 1.00 vs Group B: 2.63 ± 0.80, $P = 0.45$ Group A: 78.7% vs Group B: 81.4%, $P = 0.80$ Group A: 96.9% (126/130) vs Group B: 99.2% (131/132), $P = 0.37$	Off-pump CABG is safe to perform in poorly controlled diabetes patients (adequacy of control determined by preoperative HbA1c levels) There were no significant differences in postoperative outcomes, incidence of harvest site infection or duration of postoperative hospital stay in either group

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Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
	n = 47 - Group B: HbA1c >6.5% poorly controlled, *n* = 54, *P* = 0.0001 Follow-up: - Mean 2.4 ± 1.6 years	Stenosis free rate	Group A: 92.3% (120/130) Group B: 93.1% (123/132), *P* = 0.82	Limitations: (i) Retrospective review with a small sample size (ii) LOS postoperatively was longer than in previous reports due to routine angiograms screening 7–10 days after surgery
		Postoperative AF	Group A: 29.7% (*n* = 14) vs Group B: 22.2% (*n* = 12), *P* = 0.49	
		Wound dehiscence	Group A: 4.3% (*n* = 2) vs Group B: 9.3% (*n* = 5), *P* = 0.44	
		Postoperative hospital stay	Group A: 22.1 ± 9.5 days vs Group B: 21.7 ± 9.1 days, *P* = 0.86	
		Mortality	There were no reports of intraoperative, hospital or late cardiac deaths, *P* = 0.99	
Hudson *et al*. (2010), Can J Anesth, USA [8] Retrospective observational study (level 3b)	Single centre Sample size: - 1474 non-diabetic patients underwent primary, elective CABG - HbA1c levels were documented preoperatively - 31% (*n* = 456) patients had elevated HbA1c levels >6% All patients underwent CPB for CABG/valve procedures Non-diabetics	30-day mortality per unit increase in HbA1c	OR 1.53, CI (1.24–1.91), *P* = 0.0005	Elevated preoperative HbA1c levels is common in non-diabetics undergoing CABG. There is an independent and significant increase in early mortality risk after elective CABG of 53% per unit increase in HbA1c
		Acute kidney injury [≥50% postoperative increase from baseline creatinine to peak postoperative creatinine level in first 10 days after surgery (*n* = 1230) (83% of patients)]	AKI independently associated with elevated baseline HbA1c: *P* = 0.04, OR 1.148, 95% CI 1.003–1.313	Elevated HbA1c was associated with a significant increased risk in AKI. It predicted higher fasting and peak intraoperative glucose levels
		Infection risk: Either: +blood culture/ harvest site infection/ mediastinitis/ pneumonia/UTI	No significant association (*P* = 0.48)	Limitations: (i) Potential for selection bias as non-diabetic patients were selected in a non-randomized fashion for preoperative HbA1c testing
		Patients with HbA1c >6% were significantly: - Heavier (90 ± 22 vs 84 ± 21 kg, *P* <0.0001) - Greater incidence obesity: BMI 30.1 ± 7.7 vs 28.1 ± 6.4 kg m^{-2}, *P* <0.0001		
		- More often Caucasian than African American 88 vs 77%, *P* <0.0001		
		Blood glucose levels in HbA1c >6% vs HbA1c ≤6%: - Baseline fasting	129 ± 40 mg/dl^{-1} (7.2 ± 2.2 mmol/l^{-1}) vs 113 ± 34 mg/dl^{-1} (6.3 ± 1.9 mmol/dl^{-1}), respectively; *P* <0.0001	
		- Intraoperative peak	216 ± 57 mg/dl^{-1}	

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BEST EVIDENCE TOPIC

Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
			(12.0 ± 3.2 mmol/l^{-1}) vs 209 ± 55 mg/dl^{-1} (11.6 ± 3.1 mmol/dl^{-1}), respectively, $P = 0.03$ Baseline: correlation with HbA1c: $r = 0.30$; $P < 0.001$ Peak blood glucose correlation with HbA1c: $r = 0.8$, $P = 0.004$	
Knapik *et al*. (2011), Eur J Cardiothorac Surg, Poland [9] Retrospective review (level 3b)	Sample size: - 2665 patients underwent CABG: - 782 (29.3%) had DM Of which: - 735 (94%) of patients had HbA1c levels measured preoperatively - 341 (46.4%) on insulin - 290 (39.5%) oral medications - 104 (14.1%) diet controlled Elevated HbA1c >7% were present in 38.4% of DM patients For comparison of outcomes patients were matched to achieve similar preoperative status with a use of a Greedy matching procedure	Morbidity Stroke, wound infection, renal failure and perioperative myocardial infarction LOS: - Intensive care unit (matched comparison) - Mean LOS (matched comparison) Use of CPB in HbA1c >7% vs HbA1c ≤7%	Elevated HbA1c >7% significantly increased the frequency of perioperative MI (after matching procedure) 4.7% HbA1c >7% (±95% CI ± 3.18%) vs 0.6% HbA1c ≤7% (±95% CI ± 1.15%), $P = 0.01$ All other measured outcomes showed no significant difference and were similar in both groups 1.6 ± 2.1 days with normal HbA1c vs 1.7 ± 2.5 days elevated HbA1c, $P = 0.94$ Not significant 7.4 ± 4.4 days for normal HbA1c vs 7.7 ± 5.4 days for group with elevated HbA1c, $P = 0.59$ Not significant 194/282 (69%) vs 257/453 (57%), $P = 0.001$ Use of CPB is significantly higher in those patients with elevated HbA1c >7%	Elevated preoperative HbA1c levels have a low predictive value for mortality and complications in the early postoperative period Elevated HbA1c levels only influenced one postoperative outcome (MI) in diabetic patients Limitations: (i) Lack of mid-and long-term results (ii) Study may not have had sufficient sample size to confirm impact of elevated HbA1c is not just limited to perioperative MI The results obtained after the matching procedure were not statistically different
Tsuruta *et al*. (2011), J Cardiol, Japan [10] Prospective study (level 2b)	893 patients underwent primary, isolated, off-pump CABG 306 diabetic patients were subdivided into 3 groups according to preoperative HbA1c levels: - Group A: HbA1c <6.5% (115; mean 5.8 ± 0.4%) - Group B: HbA1c ≥6.5% but 7.5% (96; mean 6.9 ± 0.3%) - Group C:	All-cause mortality Cardiac mortality - (MI, arrhythmia, congestive heart failure or sudden death) Morbidity: - Stroke, mediastinitis, low output syndrome, arrhythmia (paroxysmal AF) Long-term outcomes according to preoperative HbA1c:	No perioperative deaths were recorded The frequency of complications was greater in Group C. However, there were no significant differences detected among the three groups There is no significant difference between all three groups for cardiac mortality and all-cause	Preoperative HbA1c levels may not be a reliable predictor of long-term outcomes for diabetic patients undergoing CABG HbA1c levels were not significantly associated with long-term mortality or morbidity outcomes in diabetic patients Limitations: (i) Not a randomized control study (ii) Postoperative changes in HbA1c were not documented

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Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
	HbA1c ≥7.5% (95; mean 8.5 ± 0.9%)	- Cardiac mortality - All-cause mortality	mortality (P = 0.17 and P = 0.26, respectively)	
Alserius *et al*. (2008), Scand Cardiovasc J, Sweden [11] Prospective study (level 2b)	605 patients underwent primary, elective primary CABG CPB used in all cases 161 (27%) patients had a diagnosis of type 2 DM - 109/161 (68%) had HbA1c ≥6% 444 non-diabetics - 13/ 444 (3%) of patients without DM had a HbA1c ≥6% Follow-up: Average 3.5 years (range 2.3–4.6)	Incidence of superficial sternal wound infection: - HbA1c ≥6% vs HbA1c <6% Incidence of mediastinitis: - HbA1c ≥6% vs <6% - DM vs no DM Follow-up mortality: - 3.5 years (range 2.3–4.6)	13.9% (17/122) if HbA1c ≥6% vs 5.2% (25/483) when HbA1c <6%, P = 0.007 Occurred more frequently if HbA1c ≥6% 4.9% (5/122) in patients with HbA1c ≥6% vs 2.1% (10/483) in HbA1c <6%, P = 0.20 HR 1.9, 95% (CI 0.6–5.9) Not significant Mediastinitis: 5% DM (8/161) vs 1.8% (8/444) of patients without DM, P = 0.03 All-cause mortality: 18.9% (23/122) HbA1c ≥6% vs 4.1% (20/483) HbA1c <6%, P <0.001 HR 5.4 (95% CI: 3–10) (Following multivariable adjustment)	3 years after CABG the mortality rate was significantly higher for those patients with a HbA1c ≥6% HbA1c ≥6% was associated with a significant increase in risk of sternal wound infection in the postoperative period. In addition, there was a trend for higher rates of mediastinitis
McGinn *et al*. (2011), J Cardiothorac Surg, USA [12] Retrospective observational review (level 3b)	1045 patients underwent CABG: - 415/1045 (40%) had a known history of DM - 630/1045 (60%) had no known history of DM Group A: 207/630 (32.9%) non-diabetic patients had HbA1c in the normal range HbA1c <5.7% Group B: 356/630 (56.5%) had an HbA1c in the increased risk for diabetes range HbA1c 5.7–6.4% Group C: 67/630 (10.6%) had an HbA1c in the diabetic range HbA1c ≥6.5%	Number of vessels revascularized: - Group C with HbA1c ≥6.5% vs Group A + B, normal/pre-diabetic group Risk factors predictive of elevated HbA1c: - Mean BMI	Group C: mean 3.6 vs Group A + B mean 3.1, P = 0.009 Newly diagnosed diabetics had a larger BMI (mean 29.5) than did those in normal (mean 27.7) and pre-diabetic Groups (mean 28.5), P = 0.031	Elevated HbA1c levels irrespective of a previous history of diabetes was significantly associated with severe disease of the coronary arteries There is a high prevalence of undiagnosed dysglycaemia in patients without a previous history of diabetes undergoing coronary revascularization

IV: intravenous; FBG: fasting blood glucose; BM: Boehringer Mannheim; FFP: fresh frozen plasma; UTI: urinary tract infection; DM: diabetes mellitus.

Conflict of interest: none declared.

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eComment. Interpretation of the data together with the management of cardiac surgery patients with diabetes mellitus

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doi: 10.1093/icvts/ivt470

We have read with interest the analysis by Tennyson *et al.* of the role of HbA1c in predicting the mortality and morbidity outcomes in patients undergoing coronary artery bypass surgery (CABG) [1].

In such patients, higher fasting blood glucose (FPG) levels are associated with a higher incidence of arrhythmia, atelectasis and prolonged mechanical ventilation, whereas higher HbA1c levels are associated with a higher incidence of intra-aortic balloon counterpulsation, massive bleeding and multi-organ failure [2]. Although diabetes mellitus (DM) is traditionally known to be associated with an increased risk for CABG, there are also adverse outcomes reported in the literature indicating similar hospital mortality rates for diabetic and non-diabetic patient groups [3]. In fact, delaying the surgical procedure seems to be the safest measure when quadrupled mortality for CABG is noted with HbA1c values of over 8.6% [1]. Since the lifespan of red blood cells is around three months, any effective change in HbA1c levels will be assumed to take place within 10-12 weeks. So, the question is about which parameters we are able to manipulate in a patient with altered FBG levels who are candidates for a CABG procedure and how we can interpret and evaluate the HbA1c and FPG levels in these patients. In our clinical practice we put all DM patients who are on oral hypoglycaemic drugs onto dual insulin treatment in the preoperative period without taking HbA1c levels into account. We encourage adequate oral hydration until the day of surgery. In the same time period, we administer moderate to high doses of oral N-acetyl cysteine (up to 2400 mg/day) for renal protection. Where the insulin-dependent patients are concerned, we check the HbA1c level. When the HbA1c level is below 6.5%, we take the same precautions for renal function and continue on the same insulin dosage. When the HbA1c level is above 6.5%, we begin with quadruple insulin therapy. In any patient with a HbA1c level above 8.5%, we delay the surgery for an average of one week from instituting the dosage of quadruple insulin. In all cases, we aim to keep the postprandial blood glucose level below 150 mg/dl and the FPG level below 110 mg/dl. During the postoperative course, we keep patients on continuous insulin infusion with regard to the close follow-up of the blood glucose level. When patients achieve adequate oral intake, we wean them from intravenous insulin infusion and onto a subcutaneous regimen. In all patients with a previous oral anti-diabetic drug usage history, we administer dual or quadruple insulin for at least three months. In our opinion, providing effective blood glucose level management and taking renal protection measures until the day of CABG surgery is as important as preoperative HbA1c levels in these patients.

Conflict of interest: none declared.

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