Journal of Cardiology (2012) 59, 275–284

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/jjcc

Original article

Impact of diabetes mellitus on outcomes in Japanese patients undergoing coronary artery bypass grafting☆

Kenji Minakata (MD, PhD)[a], Ko Bando (MD, PhD)[b], Shuichiro Takanashi (MD, PhD)[c], Hiroaki Konishi (MD, PhD)[d], Yoshihiro Miyamoto (MD, PhD)[e], Kenji Ueshima (MD, PhD, FJCC)[a], Tosiya Sato (PhD)[f], Yuichi Ueda (MD, PhD)[g], Yutaka Okita (MD, PhD)[h], Izuru Masuda (MD, PhD)[i], Hitoshi Okabayashi (MD, PhD)[j], Hitoshi Yaku (MD, PhD, FJCC)[k], Shinji Yasuno (MD, PhD)[a], Hiroyuki Muranaka (MD, PhD)[a], Masato Kasahara (MD, PhD)[a], Shigeki Miyata (MD, PhD)[e], Yoshitaka Okamura (MD, PhD)[l], Michihiro Nasu (MD, PhD)[m], Kazuo Tanemoto (MD, PhD)[n], Koichi Arinaga (MD, PhD)[o], Yosuke Hisashi (MD)[p], Ryuzo Sakata (MD, PhD, FJCC)[a,*], the JMAP Study Investigators

[a] *Kyoto University Graduate School of Medicine, Kyoto, Japan*
[b] *International University of Health and Welfare, Tochigi, Japan*
[c] *Sakakibara Heart Institute, Tokyo, Japan*
[d] *Jichi Medical University, Tochigi, Japan*
[e] *National Cerebral and Cardiovascular Center, Osaka, Japan*
[f] *Kyoto University School of Public Health, Kyoto, Japan*
[g] *Nagoya University Graduate School of Medicine, Nagoya, Japan*
[h] *Kobe University Graduate School of Medicine, Kobe, Japan*
[i] *Takeda Preventive Medicine & EBM Center, Kyoto, Japan*
[j] *Iwate Medical University, Morioka, Japan*
[k] *Kyoto Prefectural University of Medicine, Kyoto, Japan*
[l] *Wakayama Medical University, Wakayama, Japan*
[m] *Kobe City Medical Center General Hospital, Kobe, Japan*
[n] *Kawasaki Medical School, Kurashiki, Japan*
[o] *Kurume University School of Medicine, Kurume, Japan*
[p] *Kagoshima University Graduate School of Medicine and Dental Science, Kagoshima, Japan*

Received 29 October 2011; received in revised form 7 December 2011; accepted 8 December 2011
Available online 27 March 2012

☆ This paper was presented at the late breaking clinical trial session of the 75th Annual Scientific Meeting of the Japanese Circulation Society in Yokohama, Japan (August 4, 2011).

* Corresponding author at: Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. Tel.: +81 75 751 3780; fax: +81 75 751 3098.
E-mail address: sakatar@kuhp.kyoto-u.ac.jp (R. Sakata).

0914-5087/$ – see front matter
doi:10.1016/j.jjcc.2011.12.009

KEYWORDS
Complication;
Coronary artery bypass grafting;
Diabetes mellitus;
Infection;
Mortality;
Renal insufficiency

Summary
Background and purpose: There have been no large-scale studies on the impact of diabetes mellitus (DM) on outcomes in Japanese patients undergoing coronary artery bypass grafting (CABG).
Methods and subjects: A multi-institutional retrospective cohort study was conducted in 14 Japanese centers. All adult patients who underwent isolated CABG from 2007 to 2008 were included ($n = 1522$, mean age: 68.5 years). The definitions of DM were all patients admitted with diagnosis of DM and preoperative glycated hemoglobin (Hb) A1c $\geq$ 6.5%. Univariate and multivariate analyses were performed to identify the risk of morbidity and mortality.
Results: There were 849 DM and 572 non-DM patients. Preoperative mean HbA1c were 7.1% in the DM group and 5.7% in the non-DM group ($p < 0.0001$). Preoperative, intraoperative, and 3-day average postoperative blood glucose (BG) were 146 mg/dl, 172 mg/dl, and 168 mg/dl in the DM group, and 103 mg/dl, 140 mg/dl, and 136 mg/dl in the non-DM group (all $p < 0.0001$). Although there were no significant differences in postoperative cardiovascular events, the incidence of infection was significantly higher in the DM group than in the non-DM group (9.2% vs 6.1%, $p = 0.036$) on the univariate analysis. The all-cause death was also relatively higher in the DM group than in the non-DM group (2.1% vs 1.1%, $p = 0.12$), and this was likely related to infection.
Conclusion: DM patients had worse perioperative BG control, higher incidence of infection, and higher mortality than non-DM patients. These results indicate that perioperative BG control guidelines should be standardized to obtain better surgical outcomes in Japanese DM patients.

Introduction

The prevalence of diabetes mellitus (DM) has increased dramatically in Western countries over the past several decades, leading in turn to increased mortality due to cardiovascular events [1]. This trend is also apparent in Asian countries, especially in Japan, where the number of DM patients has increased from 6.9 million to 8.9 million in the past decade (a 29% increase) [2]. The most important life-threatening complication in DM patients is obviously coronary artery disease [3]. There has been debate regarding the optimal treatment for DM patients; some physicians favor percutaneous catheter intervention (PCI), while others favor coronary artery bypass grafting (CABG). Some studies have shown that CABG yields better long-term outcomes in DM patients with multivessel disease [4,5]. However, it is well known that patients with DM who undergo CABG have worse early and late outcomes than CABG patients without DM [6,7]. Also, it has been shown that intraoperative and postoperative blood glucose (BG) control has a significant effect on complications such as infection and mortality [8—10]. However, there have been no large-scale studies on Japanese DM patients undergoing CABG. To better understand the impact of DM on coronary artery surgery and to establish the optimal BG control method during cardiac surgery, we organized a multicenter/multidisciplinary research group, which we called the JMAP study group (Japanese Study to Explore the Impact of Diabetes on Cardiac Surgery for Optimal Glycemic Control Protocol). Herein, we carried out a retrospective cohort study to identify the impact of DM and BG control on surgical outcomes in Japanese patients undergoing CABG.

Materials and methods

From 2007 to 2008, a total of 1522 patients underwent isolated CABG in 14 cardiac surgery centers including 10 university hospitals (Appendix I) in Japan. Patients who underwent redo CABG were included, but patients who underwent concomitant procedures such as valvular procedures, aneurysm repair, arrhythmia surgery, repair of ventricular septal perforation, and surgical ventricular restoration procedures were excluded from this study. The number of the cases enrolled in each hospital varied from 8 to 365, also the number of the operating surgeons ranged from one to three. All the patient characteristics and operative data were extracted from the prospective national database (the Japan Adult Cardiovascular Surgery Database: JACVSD), which is similar to the Society of Thoracic Surgeons (STS) national database in North America. Other study-specific data like preoperative glycated hemoglobin (Hb)A1c and perioperative BG control, as well as other blood laboratory data and postoperative complications including cardiovascular events and individual infections, which are not included in the JACVSD, were obtained from medical records at each study site. These two sets of data were merged, then blinded, and sent to a data center (the EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan).

Demographic variables are listed in Appendix II. Of note, the Japanese Diabetes Society (JDS) value of HbA1c (%) is converted into the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the following formula according to the JDS guidelines [11]:

$$\text{HbA1c (NGSP)}\,(\%) = \text{HbA1c (JDS)}\,(\%) + 0.4\,(\%)$$

Postoperative variables were acute myocardial infarction (MI), cerebrovascular events, acute renal failure, and other cardiovascular events (including cardiac tamponade, ventricular tachycardia or fibrillation, and complications after PCI). Postoperative infection was categorized into deep sternal wound infection (anterior mediastinitis), superficial sternal wound infection, graft harvesting site infection, blood stream infection, urinary tract infection, and

pneumonia. Details of the definitions of the clinical events are summarized in Appendix III. Hospital death included all-cause death within 30 days of operation or during initial hospitalization. All the aforementioned clinical events were evaluated at the participating centers, and then assessed by the independent clinical events evaluation committee (Appendix IV) if necessary. The primary composite endpoint was defined as a composite of acute MI, cerebrovascular accidents, other cardiovascular events, all infections and their related deaths. Although cardio-cerebrovascular events were thought to be important for DM patients, this prespecified primary composite endpoint was not related to DM. Thus, we added a new composite endpoint (the additional composite endpoint), which consisted of all infections, acute renal failure, and all-cause deaths, and conducted a post hoc analysis.

DM patients were defined as those patients who were admitted to the participating hospitals with a diagnosis of DM. Patients without a previous diagnosis of DM who had preoperative HbA1c $\geq$ 6.5% (NGSP) were also included [12]. The intraoperative BG was an average of 3—4 BG measurements taken during surgery. In the intensive care unit, the frequency of BG measurement was similar among the participating hospitals: BG was measured every 2—4 h in patients with intravenous continuous insulin infusion, and at least 4 times in non-diabetic patients without insulin. The postoperative 3-day BG average was a composite average of the daily mean BG levels (BG was measured up to 12 times per day following surgery) from the day of the surgery to postoperative day 3.

Perioperative BG control methods varied from hospital to hospital, however, in all the participating institutions, it was standard practice to treat hyperglycemia with continuous insulin infusion whenever BG exceeded 200 mg/dl. Preoperative renal insufficiency was defined as an increased serum creatinine level equal to or more than 2.0 mg/dl. The internal thoracic arteries were harvested by means of skeletonized fashion using the Harmonic Scalpel (Ethicon, West Somerville, NJ, USA) in most of the participating centers. In terms of intraoperative steroid use, a large amount of steroid (methylprednisolone 500—1000 mg) was primed in a cardiopulmonary bypass circuit in some centers for on-pump CABG cases. Also, some surgeons and anesthesiologists preferred to give a moderate amount of intravenous steroid (methylprednisolone 125—500 mg) immediately after starting off-pump CABG cases to prevent systemic inflammatory responses.

Statistical analyses

Baseline characteristics of the DM and the non-DM groups are described as mean $\pm$ standard deviation for continuous variables and proportions for categorical variables. *p*-Values were calculated by the *t*-test and the chi-squared test. We compared the proportions of primary and additional composite endpoints and their components between the DM and the non-DM groups. Risk ratios and associated 95% confidence intervals were calculated.

Logistic regression analyses were conducted to estimate the magnitude of the effect of DM on the additional composite endpoint, all infections, and all-cause deaths adjusted by age (in 10-year increments), gender, body mass index, congestive heart failure, renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, left ventricular ejection fraction < 50%, operative status (elective vs urgent or emergency), bilateral internal thoracic artery use, and intraoperative steroid use. Of note, these factors were prefixed before the statistical analyses. Odds ratios and their associated 95% confidence intervals were calculated. All analyses were performed with JMP 8.0 statistics software (SAS Institute Inc., Cary, NC, USA). The two-sided alpha level was set to 5%.

This study was approved by the Internal Review Board at all the participating hospitals and the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine. All the patients and their families gave written consent at the time of operation for participation in the JACVSD.

Results

A total of 1522 enrolled patients were classified into two groups: the DM group (n = 849) and the non-DM group (n = 572). Because there were no preoperative HbA1c data for 101 patients without a previous diagnosis of DM, these patients were excluded from this study. The preoperative management of BG in the DM group included subcutaneous insulin injection in 254 patients (29.9%), oral medications in 342 (40.3%), and diet regulation in 233 (27.4%). Patients' baseline characteristics are shown in Table 1. There were no differences in terms of age, gender, and body mass index (BMI). However, depressed left ventricular systolic function (ejection fraction < 50%), renal insufficiency, and peripheral artery disease were significantly higher in the DM group than in the non-DM group. On the other hand, chronic obstructive pulmonary disease was less common in the DM group. There was no difference in terms of usage of bilateral internal thoracic artery, however intraoperative administration of intravenous steroids was more common in the non-DM group. There were no differences in operative status. Off-pump technique was used frequently in both groups (about 70% of patients in each group).

Preoperative mean HbA1c were 7.1% in the DM group and 5.7% in the non-DM group (p < 0.0001). Also, preoperative fasting, intraoperative, and 3-day average postoperative BG were 146 mg/dl, 172 mg/dl, and 168 mg/dl in the DM group, and 103 mg/dl, 140 mg/dl, and 136 mg/dl in the non-DM group, respectively. At all measurement points, DM patients had significantly higher BG levels (p < 0.0001). In terms of postoperative BG control, 71% of the patients in the DM group were treated with continuous insulin infusion whereas only 22% of the patients in the non-DM group were treated with continuous insulin infusion. As shown in Table 2, the all-cause deaths were 2.1% (n = 18) in the DM group and 1.1% (n = 6) in non-DM group (p = 0.124). There was no significant difference in the primary composite endpoint, however, the additional composite endpoint was significantly higher in the DM group. In terms of complications, although there were no significant differences in the incidence of postoperative cardiovascular events and cerebrovascular accidents, the incidence of overall infection was significantly higher in the DM group than in the non-DM group (9.2% vs 6.1%,

Table 1 Patients' baseline characteristics.

Variables	DM group ($n = 849$)	Non-DM group ($n = 572$)	p-Value
Mean age (SD)	68.6 (8.4)	68.0 (10.1)	0.282
Age ≥ 75	208 (24.5%)	162 (28.3%)	0.107
Male gender	649 (76.4%)	451 (78.9%)	0.288
Preoperative HbA1c (SD)	7.1% (1.2)	5.7% (0.4)	<0.0001
Mean body mass index (SD)	23.7 (3.3)	23.4 (3.1)	0.094
Preoperative steroid use	18 (2.1%)	8 (1.4%)	0.320
Congestive heart failure	131 (15.5%)	98 (17.1%)	0.397
Renal insufficiency	117 (13.8%)	45 (7.9%)	0.001
Chronic obstructive pulmonary disease	57 (6.7%)	64 (11.2%)	0.003
Peripheral artery disease	193 (22.7%)	101 (17.7%)	0.021
Left ventricular ejection fraction < 50%	212 (26.6%)	115 (20.5%)	0.010
Operative status			
Elective	732 (86.2%)	484 (84.6%)	0.154
Urgent	76 (9.0%)	67 (11.7%)	
Emergency	41 (4.8%)	21 (3.7%)	
Bilateral internal thoracic artery use	400 (47.1%)	285 (49.8%)	0.316
Intraoperative steroid use	246 (29.0%)	200 (35.0%)	0.017
On-pump or off-pump			
On-pump	214 (25.2%)	154 (26.9%)	0.754
On-pump beating	43 (5.1%)	27 (4.7%)	
Off-pump	592 (69.7%)	391 (68.4%)	

DM, diabetes mellitus; HbA1c, glycated hemoglobin A1c.

$p = 0.036$). In particular, the incidence of deep sternal wound infection was higher in the DM group (2.0%) than in the non-DM group (1.1%) although this did not reach statistical significance ($p = 0.163$). The cause of death in the DM group was predominantly related to infection (10/18: 56%), while in the non-DM group there was only one patient who died of infection (1/6: 17%). On multivariate logistic regression analyses, the statistically significant risk factors for the

Table 2 Adverse events and outcomes.

	DM group ($n = 849$)	Non-DM group ($n = 572$)	Risk ratio (95% CI)	p-Value
Primary composite endpoint[a]	105 (12.4%)	60 (10.5%)	1.18 (0.87—1.59)	0.279
Additional composite endpoint[b]	92 (10.8%)	42 (7.3%)	1.48 (1.04—2.09)	0.027
All-cause deaths	18 (2.1%)	6 (1.1%)	2.02 (0.81—5.06)	0.124
Acute myocardial infarction	11 (1.3%)	12 (2.1%)		NA
Related death	2 (0.2%)	0		NA
Cerebrovascular accident	12 (1.4%)	6 (1.1%)		NA
Related death	1 (0.1%)	0		
Other cardiovascular event	11 (1.3%)	15 (2.6%)		NA
Related death	3 (0.4%)	1 (0.2%)		
All infections	78 (9.2%)	35 (6.1%)	1.50 (1.02—2.21)	0.036
Related death	10 (1.2%)	1 (0.2%)		
Infection site				
Deep sternal wound	17 (2.0%)	6 (1.1%)	1.91 (0.76—4.81)	0.163
Superficial sternal wound	22 (2.6%)	15 (2.6%)		
Graft harvest site	22 (2.6%)	9 (1.6%)		
Blood stream	5 (0.6%)	2 (0.4%)		
Urinary tract	5 (0.6%)	1 (0.2%)		
Pneumonia	9 (1.1%)	8 (1.1%)		
Acute renal failure	12 (1.4%)	5 (0.9%)	1.62 (0.57—4.57)	0.359
Related death	1 (0.1%)	0		
Other deaths	1 (0.1%)	4 (0.7%)		NA

CI, confidence interval; DM, diabetes mellitus; NA, not available due to too few events.

[a] Primary composite endpoint consisted of acute myocardial infarction, cerebrovascular accidents, other cardiovascular events, overall infection and their related deaths.

[b] Additional composite endpoint consisted of overall infection, acute renal failure, and all-cause deaths.

Table 3 Multivariate logistic regression analysis for the primary composite endpoint.[a]

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.07	0.75—1.53	0.715
Age (in 10-year increments)	1.01	0.83—1.23	0.915
Male gender	0.58	0.40—0.86	0.006
Body mass index (in 1 kg/m^2 increments)	1.04	0.98—1.09	0.164
Congestive heart failure	1.01	0.58—1.70	0.985
Renal insufficiency	2.18	1.36—3.43	0.001
Chronic obstructive pulmonary disease	1.73	0.98—2.95	0.051
Peripheral artery disease	1.12	0.73—1.69	0.585
Left ventricular ejection fraction < 50%	1.25	0.83—1.86	0.268
Urgent	1.71	0.95—2.97	0.065
Emergency	0.79	0.22—2.24	0.689
Bilateral internal thoracic artery use	1.34	0.94—1.91	0.105
Intraoperative steroid use	0.72	0.49—1.06	0.100

CI, confidence interval.
[a] Primary composite endpoint consisted of acute myocardial infarction, cerebrovascular accidents, other cardiovascular events, overall infection and their related deaths.

Table 4 Multivariate logistic regression analysis for the additional composite endpoint.[a]

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.28	0.85—1.92	0.235
Age (in 10-year increments)	1.01	0.81—1.26	0.935
Male gender	0.58	0.38—0.89	0.012
Body mass index (in 1 kg/m^2 increments)	1.07	1.02—1.14	0.012
Congestive heart failure	0.94	0.51—1.67	0.843
Renal insufficiency	3.23	2.00—5.14	0.000
Chronic obstructive pulmonary disease	1.91	1.02—3.41	0.034
Peripheral artery disease	0.94	0.57—1.49	0.787
Left ventricular ejection fraction < 50%	1.39	0.89—2.13	0.139
Urgent	1.60	0.82—2.95	0.149
Emergency	1.13	0.34—3.13	0.823
Bilateral internal thoracic artery use	1.31	0.89—1.94	0.177
Intraoperative steroid use	0.66	0.42—1.01	0.060

CI, confidence interval.
[a] Additional composite endpoint consisted of overall infection, acute renal failure, and all-cause death.

Table 5 Multivariate logistic regression analysis for all infections.

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.29	0.84—2.01	0.253
Age (in 10-year increments)	0.96	0.76—1.22	0.751
Male gender	0.52	0.33—0.83	0.005
Body mass index (in 1 kg/m^2 increments)	1.08	1.02—1.14	0.014
Congestive heart failure	0.96	0.49—1.79	0.904
Renal insufficiency	3.13	1.86—5.16	0.000
Chronic obstructive pulmonary disease	1.85	0.93—3.46	0.064
Peripheral artery disease	0.85	0.49—1.40	0.533
Left ventricular ejection fraction < 50%	1.42	0.88—2.26	0.142
Urgent	1.37	0.65—2.69	0.386
Emergency	0.72	0.16—2.36	0.619
Bilateral internal thoracic artery use	1.37	0.90—2.09	0.144
Intraoperative steroid use	0.68	0.42—1.06	0.099

CI, confidence interval.

Table 6 Multivariate logistic regression analysis for all-cause death.

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.89	0.72—5.61	0.219
Age (in 10-year increments)	1.10	0.67—1.88	0.715
Male gender	0.66	0.25—1.97	0.429
Body mass index (in 1 kg/m^2 increments)	0.90	0.78—1.04	0.169
Congestive heart failure	2.27	0.69—7.03	0.165
Renal insufficiency	3.04	1.12—7.80	0.023
Chronic obstructive pulmonary disease	4.22	1.24—12.60	0.013
Peripheral artery disease	1.56	0.55—4.07	0.374
Left ventricular ejection fraction < 50%	2.33	0.92—5.87	0.071
Urgent	3.15	0.89—10.32	0.065
Emergency	5.30	1.05—26.7	0.043
Bilateral internal thoracic artery use	1.85	0.71—4.81	0.204
Intraoperative steroid use	0.35	0.10—1.00	0.073

CI, confidence interval.

primary composite endpoint included female gender and renal insufficiency (Table 3). The statistically significant risk factors for the additional composite endpoint included female gender, BMI, renal insufficiency, and chronic obstructive pulmonary disease (Table 4). Also, the statistically significant risk factors for overall infection were female gender, BMI, and renal insufficiency (Table 5). Finally, the statistically significant preoperative or operative risk factors for all-cause death were renal insufficiency, congestive heart failure, and emergency surgery (Table 6). The presence of DM was not identified as a statistically significant independent risk factor on multivariate analyses for the composite endpoints and complications including overall infection and all-cause death which were linked to DM on the univariate analyses. On the other hand, it became apparent that preoperative renal insufficiency was a very strong common risk factor for both overall infection and all-cause death.

Discussion

In 2009, the Society of Thoracic Surgeons Blood Glucose Management Task Force published their guidelines regarding BG management during adult cardiac surgery [13]. According to these guidelines, it is highly desirable to maintain BG < 180 mg/dl during surgery and during the immediate postoperative period with intravenous insulin infusion in DM patients. Although it is unnecessary to use intravenous continuous insulin infusion in non-DM patients during surgery, both DM and non-DM patients benefit from maintaining BG < 180 mg/dl in order to prevent morbidity and mortality [13]. This begs the question of how low the target should be. Furnary et al. reported from their prospective observational study that there was a highly significant relationship between mortality and postoperative glucose levels rising above 175 mg/dl [10]. Our current BG levels in DM patients were barely below this cut-off value, given the intraoperative and postoperative 3-day average BG were 172 mg/dl and 168 mg/dl, respectively. Therefore, there seemed to be some room to lower the BG levels further, which potentially would reduce the morbidity and the mortality in the DM patients.

It has been reported that the presence of DM in patients undergoing CABG is a significant risk factor for hospital mortality and morbidity including stroke, deep sternal wound infection, and length of hospital stay from the STS database analyses [14]. In addition, DM patients have worse long-term survival than non-DM patients after surgery [6]. Our results from univariate analyses show that DM has a significant influence on the additional composite endpoint consisting of all-cause death, overall infection, and acute renal failure (10.8% vs 7.3%, $p = 0.027$). Looking at each complication, overall infection was the most significant factor contributing to this result (9.2% in DM group vs 6.1% in non-DM group, $p = 0.036$). Also, DM patients tended to have higher mortality than non-DM patients (2.1% vs 1.1%, $p = 0.124$). Moreover, DM patients tended to have a much higher incidence of deep sternal wound infection than non-DM patients (2.0% vs 1.1%, $p = 0.163$), although this difference did not reach statistical significance. However, the complication of infection definitely influenced mortality rates because the majority of deaths were related to infection in the DM group. There is no doubt that DM patients have unfavorable baseline characteristics such as diffuse coronary artery disease, peripheral artery disease, high BMI, and worse preoperative renal function, all of which would contribute to worse short- and long-term outcomes compared to non-DM patients.

Our multivariate logistic regression analyses failed to identify DM as an independent risk factor for any of the complications including overall infection and all-cause death. This is most likely because some other preoperative risk factors such as renal insufficiency (predominantly in the DM group) and chronic obstructive pulmonary disease (predominantly in the non-DM group) had too much influence to each endpoint, which attenuated the impact of the presence of DM. This is one of the well-known downsides of the logistic regression models. In fact, the prevalence of preoperative renal insufficiency in this study population is much higher (13.8% in the DM group) than that of other studies published in the literature [10]. It should also be noted that 85 patients (5.6% of all study patients) predominantly in the

DM group had been on chronic hemodialysis preoperatively, which must have given great impact to the multivariate analyses. We are now in the process of doing a sub-analysis in this regard to identify the relative impact of the presence of preoperative renal insufficiency.

The Portland Diabetic Project, which is an on-going prospective study of over 5000 DM patients, aims to show that tight glucose control from the end of surgery until the 2nd postoperative day with continuous insulin infusion may eliminate the diabetic disadvantage [15]. They showed that tight glucose control with a full 3 days of continuous insulin infusion (the Portland Protocol) significantly reduced mortality (by 65%), deep sternal wound infection (by 63%), and length of hospital stay (average 2-day reduction). Therefore, they concluded that DM is not the true risk factor for the seemingly unfair diabetic disadvantage in terms of increased mortality and morbidity. Since we showed that DM patients still have excess mortality and morbidity compared to non-DM patients in the current study, we might be able to reduce these excess complications by implementing tighter glucose control protocols.

It has been debated whether intensive BG control is better than conventional BG control. In a landmark paper, van den Berghe et al. conducted the first prospective randomized trial comparing tight BG control (target 80—110 mg/dl) with intensive insulin therapy to conventional BG control in critically ill surgical patients [16]. They demonstrated that tight BG control resulted in a significant reduction in mortality (10.6% with intensive treatment vs 20.2% with conventional treatment, $p = 0.005$), exclusively in those patients who required $\geq$5 days of intensive care unit (ICU) care with multiorgan failure and sepsis. Also, cardiac surgical mortality was reduced in those patients requiring $\geq$3 days of ICU care. D'Alessandro et al. reported a propensity analysis that showed that strict BG control significantly reduced the EuroSCORE expected mortality in DM patients undergoing CABG, especially in moderate- to high-risk patients [17]. Their BG target in the operating room and ICU were 150—200 mg/dl and $\leq$140 mg/dl, respectively. In terms of long-term outcomes, Lazar et al. showed that tight perioperative glucose control with glucose-insulin-potassium solution improved not only perioperative outcomes, but also long-term survival and freedom from recurrent angina [18]. These studies clearly demonstrate the superiority of tight BG control over conventional control, especially in critically ill patients. On the other hand, Gandhi et al. showed in a prospective randomized study on 400 patients undergoing CABG, including non-DM patients, that intraoperative intensive insulin therapy with a target range of 80—100 mg/dl did not reduce perioperative mortality and morbidity, but rather increased stroke rate and mortality [19]. Furthermore, a meta-analysis of 29 randomized studies focusing on the benefits and risks of tight glucose control in critically ill adult patients concluded that tight glucose control was not associated with significantly reduced hospital mortality but was associated with an increased risk of hypoglycemia [20]. To support these results, a recent prospective randomized multicenter trial (the NICE-SUGAR study) demonstrated that intensive BG control with a target of 81—108 mg/dl increased mortality among adults in the ICU compared with conventional BG control with a target of 180 mg/dl or less [21]. In this study, however, the mortalities in the intensive control group and conventional control group were 27.5% and 24.9% at 90 days after randomization, respectively. In both groups, potentially life-sustaining treatments were withheld or withdrawn in more than 90% of the patients who died. Also, it seems that severe hypoglycemia commonly occurred in the intensive BG control group of the study, which may raise the question of the safety and feasibility of the tight glucose control protocol itself. Because these patients in the study were so sick at the time of enrollment, it is difficult to compare the results of these studies with studies on regular cardiac surgery patients, given the current acceptable mortality after CABG of around 1—2%. It may be necessary to conduct a prospective randomized study to compare tight glucose control and conventional glucose control using more sophisticated protocols with a minimum risk of hypoglycemia in exclusively cardiac surgery patients to reach a definitive conclusion, which we are currently planning to initiate as a next step to our ultimate goal.

Perhaps, one of the other interesting features of this multi-center study is the fact that about 70% of all isolated CABG procedures were performed using the off-pump technique in both the DM and non-DM groups. This trend is far above the typical rates in North America, given the fact that the adoption of off-pump CABG was only 21.8% in 2009 according to the STS database [22]. A systematic review and meta-analysis of propensity score analyses in more than 123,000 patients comparing off-pump and on-pump CABG demonstrated that off-pump provides favorable outcomes in mortality, stroke, renal failure, wound infection, blood transfusion, intraaortic balloon pump support, and prolonged ventilation [23]. It will be interesting to see the impact of off-pump techniques in DM patients in terms of not only preoperative, intraoperative, and postoperative glucose control, but also in terms of postoperative complications and related mortality [24]. We are also planning to perform a post hoc subgroup analysis focusing on this in the near future.

There are several limitations to this study. This was a retrospective, observational study, and hence unknown patient selection processes may cause a bias. Importantly, there was no standard BG control protocol across the participating hospitals. Our sample size was relatively large, however, it was not large enough to stratify the level of perioperative BG control as an indicator of risk events. In fact, we were unable to show any difference in terms of the morbidity and mortality according to the level of intraoperative and postoperative BG control due to too few complications.

Conclusions

DM patients had poor perioperative BG control and higher incidence of infection with a higher mortality rate than non-DM patients. These results highlight the need to initiate prospective studies to standardize perioperative BG control protocols to obtain strict BG control, which may yield better surgical outcomes in Japanese DM patients undergoing cardiac surgery.

Acknowledgments

We are indebted to the participating centers, investigators, and clinical research coordinators for their great contributions to data collection. The centers and investigators are listed in Appendices I and IV. Also, we deeply thank the Independent Clinical Events Evaluation Committee and the External Advisory Board of this study as listed in Appendix IV. Lastly, we are grateful to the organizing committee of JACVSD.

The source of funding: This study was supported by a Health and Labour Science Research Grant from the Ministry of Health, Labour and Welfare of Japan (Grant ID: 09158533).

Appendix I. The list of the participating surgical centers

Iwate Medical University Hospital, Sakakibara Heart Institute, Jichi Medical University Hospital, Nagoya University Hospital, Handa City Hospital, University Hospital of Kyoto Prefectural University of Medicine, Kyoto University Hospital, Tominaga Hospital, Wakayama Medical University Hospital, Kobe University Hospital, Kobe City Medical Center General Hospital, Kawasaki Medical School Hospital, Kurume University Hospital, Kagoshima University Hospital.

Appendix II.

Preoperative variables include age, gender, height, and weight. Preoperative co-morbidities included systemic hypertension, dyslipidemia, insulin-controlled diabetes mellitus (DM), oral medication-controlled DM, diet-controlled-DM, congestive heart failure, renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, cigarette smoking, cerebrovascular accidents, and advanced New York Heart Association functional class. Cardiovascular variables included left main coronary disease, number of diseased coronary arteries, left ventricular ejection fraction, unstable angina, acute myocardial infarction (MI), previous MI, history of atrial fibrillation and ventricular tachycardia or fibrillation, cardiogenic shock, percutaneous coronary intervention, and intra-aortic balloon pump insertion. Preoperative blood laboratory variables included random and fasting serum glucose, glycated hemoglobin A1c, albumin, serum creatinine, blood urea nitrogen, total cholesterol, high-density and low-density lipoproteins, triglycerides, and C-reactive protein. Preoperative medications included digitalis, beta-blockers, nitrates, inotropic agents, oral hypoglycemics, insulin, diuretics, steroids, and immunosuppressants. Intraoperative variables were operative status (elective, urgent, or emergency), reoperative procedure, single or bilateral internal thoracic artery or other arterial conduit usage, saphenous vein grafts and their targets, use of cardiopulmonary bypass, application of aortic cross-clamping, aortic cross-clamp time, cardiopulmonary bypass time, administration of intravenous insulin and steroids, and blood transfusion.

Appendix III. Definitions of clinical events

Acute myocardial infarction: the presence of at least two of the following symptoms or findings:

(1) Creatine kinase (CK)-MB $\geq$ 5% of total CK and total CK $\geq 3\times$ normal control, or CK-MB $\geq$ 100 mg/dl.
(2) Typical symptoms.
(3) Typical electrocardiographic (ECG) change (new onset of ST-T change in more than 2 consecutive leads on 12-lead ECG or abnormal Q wave).
(4) New onset abnormal wall motion abnormality lasting $\geq$24 h on echocardiography.

Of note, a pathological diagnosis of acute MI on autopsy does not require any of the above findings.

Cerebral infarction: including all the following symptoms and findings:

(1) Apparent focal neurological deficits and symptoms or signs compatible with no other identified causes.
(2) Neurological symptoms and signs lasting $\geq$24 h (excluded if patient died).
(3) Radiological diagnosis on computed tomography or magnetic resonance image.

Acute renal failure: increased creatinine of more than twice the preoperative baseline and equal to or more than 2.0 mg/dl, or newly requiring hemodialysis.

Infection: infection occurs within 30 days after surgery

1. *Deep sternal wound infection*: infection involving deep sternum and/or anterior mediastinum (fascia, sternum, mediastinum) and either:
   (1) Purulent drainage from the deep incision or the chest tube which is placed in the area communicating to the anterior mediastinum.
   (2) Organisms isolated from an aseptically obtained culture of fluid or tissue from the deep sternal wound or anterior mediastinum.
   (3) A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38 °C), localized pain, or tenderness, unless site is culture-negative.
   (4) An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
   (5) Diagnosis of a deep incisional surgical site infection by a surgeon or attending physician.
2. *Superficial sternal wound infection*: infection involving only the skin or subcutaneous tissue of the incision and either:
   (1) Purulent drainage, with or without laboratory confirmation, from the superficial incision.
   (2) Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
   (3) At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is

deliberately opened by surgeon, unless the incision is culture-negative.
(4) Diagnosis of superficial incisional surgical site infection by the surgeon or attending physician.

3. *Graft harvest site infection*: surgical site(s) infection including saphenous vein and radial artery harvesting:
   (1) At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat.
   (2) Superficial incision is deliberately opened by the surgeon, or required resection of tissue or drainage, unless the incision is culture-negative.
   (3) Diagnosis of superficial incisional surgical site infection by the surgeon or attending physician.
4. *Blood stream infection*: the presence of a positive non-contaminated blood culture.

   Contamination is diagnosed if one or more of the following organisms is identified in only one of a series of blood cultures: coagulase-negative staphylococci; *Propionibacterium acnes*; *Micrococcus* species; ''viridans''-group streptococci; *Corynebacterium* species; or *Bacillus* species.
5. *Urinary tract infection*: defined as the presence of symptoms or signs compatible with no other identified source of infection along with either:
   (1) $>10^5/mm^3$ colony forming units/ml of at least one bacterial species in a single urine specimen.
   (2) purulent urine (>10 white blood cells/field in a microscopic urinalysis).
6. *Pneumonia*: The clinical suspicion of pneumonia is based on clinical criteria; new or progressive radiological pulmonary infiltrate plus more than two of the following characteristics: temperature ($38\,^\circ C <$ or $< 35.5\,^\circ C$), leukocyte count ($>12{,}000\,cells/mm^3$ or $<4000\,cells/mm^3$) or purulent respiratory secretions. Ventilator-associated pneumonia is diagnosed in patients with microbiologic evaluation including the collection of at least one lower respiratory airway sample by sputum, tracheobronchial aspirate, bronchoscopy or by blind bronchoalveolar lavage. Blood cultures and cultures of pleural fluid specimens, if puncture was indicated, were also undertaken. Microbiologic confirmation of pneumonia was defined by the presence of ≥ 1 potentially pathogenic microorganism in the respiratory samples above the predefine thresholds (for bronchoalveolar lavage specimens, $>10^4$ colony forming units/ml; for sputum or tracheobronchial aspirate specimens, $>10^5$ colony forming units/ml); in pleural fluid specimens; or in blood cultures, if an alternative cause of bacteremia was ruled out.

Appendix IV.

Other investigators: Yoshino Mitsunaga (Iwate Medical University), Shigefumi Matsuyama (Sakakibara Heart Institute), Shin-ichi Mizutani (Nagoya University Graduate School of Medicine), Akira Fujimoto, Mariko Nakamoto, Masami Fukutomi, Koji Oba (Kyoto University Graduate School of Medicine), Kiyoshi Doi (Kyoto Prefectural University of Medicine), Yuki Okamoto (Tominaga Hospital), Kentaro Honda (Wakayama Medical University), Kenji Okada (Kobe University Graduate School of Medicine), Yu Shomura (Kobe City Medical Center General Hospital), Eiichi Tejima (Kawasaki Medical School), Masahiro Ueno (Kagoshima University Graduate School of Medicine and Dental Science).

Independent Clinical Events Evaluation Committee: Yutaka Ohiso, MD, PhD, Toyoaki Murohara, MD, PhD (Nagoya University Graduate School of Medicine), Kohei Kaku, MD, PhD, Kazumi Kimura, MD, PhD, Kiyoshi Yoshida, MD, PhD (Kawasaki Medical School), Kazuo Kimura, MD, PhD (Yokohama City University), Yutaka Furukawa, MD, PhD (Kobe City Medical Center General Hospital), Kotaro Mitsutake, MD, PhD (Saitama Medical University).

External Advisory Board: Soichiro Kitamura, MD, PhD (National Cerebral and Cardiovascular Center), Hiroo Imura, MD, PhD (Foundation for Biomedical Research and Innovation), Masato Kasuga, MD, PhD (National Center for Global Health and Medicine), Haruhiko Kikuchi, MD, PhD (Kobe City Medical Center General Hospital), Ryozo Nagai, MD, PhD (University of Tokyo), Yoshio Yazaki, MD, PhD (National Hospital Organization), Anthony P. Furnary, MD (Providence St. Vincent Medical Center, Portland, OR, USA).

References

[1] Bonow RO, Gheorghiade M. The diabetes epidemic: a national and global crisis. Am J Med 2004;116(Suppl. 5A):2S—10S.
[2] Annual report from the national survey of life and nutrition 2007. The Ministry of Health, Labour and Welfare of Japan (Japanese). Available at http://www.mhlw.go.jp/houdou/2008/12/h1225-5.html.
[3] Flaherty JD, Davidson CJ. Diabetes and coronary revascularization. JAMA 2005;293:1501—8.
[4] Brener SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS. Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. Circulation 2004;109:2290—5.
[5] Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrié D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, Kähler J, Kelsey SF, King SB, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 2009;373:1190—7.
[6] Szabó Z, Håkanson E, Svedjeholm R. Early postoperative outcome and medium-term survival in 540 diabetic and 2239 nondiabetic patients undergoing coronary artery bypass grafting. Ann Thorac Surg 2002;74:712—9.
[7] Carson JL, Scholz PM, Chen AY, Peterson ED, Gold J, Schneider SH. Diabetes mellitus increases short-term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. J Am Coll Cardiol 2002;40:418—23.
[8] Doenst T, Wijeysundera D, Karkouti K, Zechner C, Maganti M, Rao V, Borger MA. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg 2005;130:1144.
[9] Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg 1999;67:352—60.
[10] Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, Floten HS, Starr A. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003;125:1007—21.

[11] The Committee of Japan Diabetes Society on the diagnostic criteria of diabetes mellitus. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Invest 2010;1:212—28.
[12] Gillett MJ. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327—34.
[13] Lazar HL, McDonnell M, Chipkin SR, Furnary AP, Engelman RM, Sadhu AR, Bridges CR, Haan CK, Svedjeholm R, Taegtmeyer H, Shemin RJ, Society of Thoracic Surgeons Blood Glucose Guideline Task Force. The Society of Thoracic Surgeons Practice Guideline Series: blood glucose management during adult cardiac surgery. Ann Thorac Surg 2009;87:663—9.
[14] Brown JR, Edwards FH, O'Connor GT, Ross CS, Furnary AP. The diabetic disadvantage: historical outcomes measures in diabetic patients undergoing cardiac surgery — the pre-intravenous insulin era. Semin Thorac Cardiovasc Surg 2006;18:281—8.
[15] Furnary AP, Wu Y. Eliminating the diabetic disadvantage: the Portland Diabetic Project. Semin Thorac Cardiovasc Surg 2006;18:302—8.
[16] van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345:1359—67.
[17] D'Alessandro C, Leprince P, Golmard JL, Ouattara A, Aubert S, Pavie A, Gandjbakhch I, Bonnet N. Strict glycemic control reduces EuroSCORE expected mortality in diabetic patients undergoing myocardial revascularization. J Thorac Cardiovasc Surg 2007;134:29—37.
[18] Lazar HL, Chipkin SR, Fitzgerald CA, Bao Y, Cabral H, Apstein CS. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. Circulation 2004;109:1497—502.
[19] Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, Johnson MG, Williams AR, Cutshall SM, Mundy LM, Rizza RA, McMahon MM. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med 2007;146:233—43.
[20] Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA 2008;300:933—44.
[21] Study Investigators NICE-SUGAR, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283—97.
[22] The Society of Thoracic Surgeons. Adult cardiac surgery database executive summary. Available at http://www.sts.org/sts-nationaldatabase.
[23] Kuss O, von Salviati B, Börgermann J. Off-pump versus on-pump coronary artery bypass grafting: a systemic review and meta-analysis of propensity score analyses. J Thorac Cardiovasc Surg 2010;140:829—35.
[24] Tsuruta R, Miyauchi K, Yamamoto T, Dohi S, Tambara K, Dohi T, Inaba H, Kuwai K, Daida H, Amano A. Effect of preoperative hemoglobin A1c levels on long-term outcomes for diabetic patients after off-pump coronary artery bypass grafting. J Cardiol 2011;57:181—6.