Impact of preoperative glycometabolic status on outcomes in cardiac surgery: Systematic review and meta-analysis

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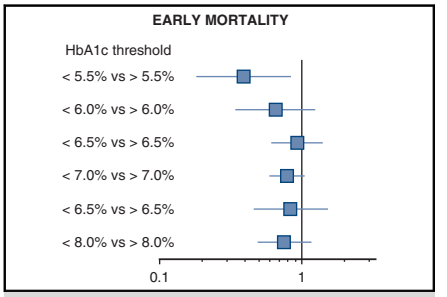
ABSTRACT

Background: Historically, impaired glucose metabolism has been associated with early and late complicated clinical outcomes after cardiac surgery; however, such a condition is not specific to subjects with diabetes mellitus and involves a larger patient population.

Methods: Databases were screened (January 2000 to December 2020) to identify eligible articles; studies that evaluated the association between preoperative metabolic status, as assessed by glycosylated hemoglobin levels and clinical outcomes, were considered. The studies were stratified in thresholds by baseline glycosylated hemoglobin level (lower vs higher).

Results: Thirty studies, involving 34,650 patients, were included in the review. In a meta-analysis stratified by glycosylated hemoglobin levels, early mortality was numerically reduced in each threshold comparison and yielded the highest reductions when less than 5.5% versus greater than 5.5% glycosylated hemoglobin levels were compared (risk ratio, 0.39; 95% confidence interval, 0.18-0.84; $P = .02$). Comparing higher glycosylated hemoglobin threshold values yielded comparable results. Late mortality was reduced with lower levels of glycosylated hemoglobin. Low preoperative glycosylated hemoglobin was associated with the lowest risk of sternal wound infections (risk ratio, 0.50; 95% confidence interval, 0.32-0.80; $P = .003$ and risk ratio, 0.53; 95% confidence interval, 0.39-0.70; $P < .0001$) for comparisons of less than 7.5% versus greater than 7.5% and less than 7.0% versus greater than 7.0% glycosylated hemoglobin thresholds, respectively. Additionally, levels of glycosylated hemoglobin lower than 7% were associated with reduced hospital stay, lower risk of stroke/transient ischemic attack (risk ratio 0.53; 95% confidence interval, 0.39-0.70; $P < .0001$), and acute kidney injury (risk ratio, 0.65; 95% confidence interval, 0.54-0.79; $P < .0001$).

Conclusions: Lower levels of glycosylated hemoglobin in patients undergoing cardiac surgery are associated with a lower risk of early and late mortality, as well as in the incidence of postoperative acute kidney injury, neurologic complications, and wound infection, compared with higher levels. (J Thorac Cardiovasc Surg 2022;164:1950-60)



Reduction of risk for early mortality in patients with preoperative optimal glycemic control.

CENTRAL MESSAGE

A J-shaped relationship exists between lower values of preoperative HbA1c and lower risk of early and late mortality after surgery, as well as in the incidence of preoperative AKI, stroke/TIA, and sternal wound infection.

PERSPECTIVE

This meta-analysis of 30 studies, including approximately 35,000 patients, found that compared with lower thresholds of HbA1c, higher preoperative HbA1c levels were associated with an increased risk of postoperative mortality and morbidity in patients who underwent cardiac surgery. Therefore, intensive HbA1c lowering is advisable to reduce the operative risk for worse outcomes.

See Commentaries on pages 1961 and 1963.

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Abbreviations and Acronyms

AKI = acute kidney injury
CABG = coronary artery bypass grafting
CI = confidence interval
DM = diabetes mellitus
HbA1c = glycosylated hemoglobin
MD = mean difference
MI = myocardial infarction
RR = risk ratio
TIA = transient ischemic attack

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Diabetes mellitus (DM) is one of the most challenging concerns for public health. According to the latest 2016 data from the World Health Organization, an estimated 422 million of adults are affected by DM.[1] Patients with DM have a 2- to 4-fold increase in the risk of developing cardiovascular disease than those without DM and a 2- to 5-fold increased mortality due to cardiovascular disease when compared with age- and sex-matched persons without DM.[2]

Patients with DM represent approximately 25% of subjects undergoing coronary revascularization,[3] and coronary artery bypass grafting (CABG) is the preferred method of revascularization for this subgroup of patients in the presence of multivessel coronary disease.[4-7] Previous studies have clearly demonstrated that high perioperative blood glucose levels are associated with an increased incidence of postoperative complications and reduced survival after CABG.[8,9] Yet, hyperglycemia on random serum samples does not necessarily reflect the long-term status of glycometabolic control being potentially influenced by several concomitant factors, including underlying diseases and related treatments leading to hospitalization.[10] Hyperglycemia has been reported to act as a strong predictor of both morbidity and mortality in subjects without a previous diagnosis of DM undergoing cardiac surgery.[11] An adjunctive potentially confounding factor may be underdiagnosis and consequent underestimation of DM in the general population.[12]

Measuring glycosylated hemoglobin (HbA1c) levels preoperatively is the method of choice for defining glycometabolic status because it reflects blood glucose levels of the 2 to 3 months before the assessment.[13] The American Diabetes Association currently advocates that diabetic subjects should achieve target HbA1c levels less than 7% because it is associated with a lower risk of diabetes-related complications.[13]

Several studies have evaluated the potential clinical implications of HbA1c levels in diabetic and nondiabetic patients undergoing cardiac surgery. However, most of these studies were retrospective in design, with no adequate statistical power, due to the relatively small sample size, to draw definitive conclusions. Therefore, we performed a systematic review and meta-analysis of the existing literature to evaluate whether baseline preoperative glycometabolic status, as assessed by serum HbA1c levels, is associated with the early and long-term cardiac surgery outcomes reductions.

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted in accordance to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines[14] and registered in PROSPERO (International Prospective Register of Systematic Reviews) (ID: CRD42020160942). The need for ethical approval and consent was waived for this systematic review.

Search Strategy and Data Extraction

MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched for eligible studies from January 1, 2000, to December 31, 2020. Keywords pertinent to the exposure of interest were used in relevant combinations: "cardiac surgery," "open-heart surgery," "hyperglycemia," "glycemic control," "glucose variability," "glycated hemoglobin," "glycosylated hemoglobin." The literature search was limited to articles published in English. Reference lists were reviewed manually and cross-checked for other relevant reports.

Randomized controlled trials, prospective, and retrospective observational cohort studies that compared clinical outcomes in patients undergoing cardiac surgery based on preoperative glycometabolic control, as assessed by glycated hemoglobin (HbA1c) thresholds, were included in our analysis.

Studies were excluded if they met one of the following exclusion criteria: (1) pediatric (age <18 years) and congenital heart surgery–related studies; (2) reviews or case reports; (3) nonhuman studies; (4) studies or arms in which HbA1c levels could not be ascertained or was reported as continuous variable; (5) studies not reporting the clinical outcomes of interest. In case of multiple publications on the same patient cohort and institution, the most complete study in terms of outcome and patient information was selected for reporting, unless providing, separately, long-term follow-up.

Titles, abstracts, and full-text articles were independently reviewed by 2 investigators (C.C. and M.M.) against the specified inclusion criteria. Discrepancies were resolved through consensus and consultation with a third investigator (R.L.). Two reviewers (C.C. and M.M.) extracted data from the selected studies by using a standardized form, and a third investigator (R.L.) checked the collected data for completeness and accuracy.

Outcome Measures and Quality Assessment

The primary outcome of this meta-analysis was early mortality, defined as any death, regardless of cause, occurring in-hospital or within 30 days after surgery; death occurring after 30 days during was only considered if during the index hospitalization subsequent to the surgery. Secondary outcomes included postoperative complications: acute kidney injury (AKI), sternal wound infection, cerebrovascular events inclusive of stroke or transient ischemic attack (TIA), and myocardial infarction (MI). Outcome definitions were adopted as for the included studies. Additionally, we meta-analyzed the postoperative length of hospital stay and late (>1 year) mortality.

The quality assessment of included studies has been performed in accordance with the recommendations given by the Cochrane Prognosis Methods Group for evaluating risk of bias in prognostic factor studies; thus, risk of bias at the individual study level was assessed using the Quality In Prognosis Studies tool.[15,16]

Statistical Analysis

Statistical analysis was performed using Review Manager version 5.3.5 (The Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-Analysis 2.2 (Biostat, Englewood, NJ). The Cochran's Q test and I^2 test were performed to judge the heterogeneity among the studies included in the meta-analysis. Heterogeneity was also considered to be significant at P less than .10 for the Q statistic. An I^2 value less 40% indicates low heterogeneity, values between 40% and 70% suggest moderate heterogeneity, and I^2 greater than 70% were considered high heterogeneity. To best account for within- and between studies variance, pooled analyses were performed by the random-effects model. Studies reporting outcomes of interest were included in subgroups representing thresholds of preoperative glycometabolic control: (1) HbA1c less than 5.5% versus more than 5.5%; (2) less than 6.0% versus more than 6.0%; (3) less than 6.5% versus more than 6.5%; (4) less than 7.0% versus more than 7.0%; (5) less than 7.5% versus more than 7.5%; and (6) less than 8.0% versus more than 8.0%. The data were assigned to specific thresholds based on the stratification applied in the original study. Pooled risk ratios (RRs) were reported with 95% confidence intervals (CIs) for each subgroup. For the analysis of length of hospital stay, mean difference (MD) along with 95% CIs is reported. Whenever applicable, median and interquartile ranges were converted to mean ± standard deviation according to Wan and colleagues.[17] RRs per person-years accounting for potential differences in follow-up are reported for the more than 1 year mortality again for each threshold comparison. Publication bias was examined by the visual assessment of funnel plots[18] and by Egger's regression. Additionally, by means of meta-regression, we addressed potential relationships between early mortality and baseline characteristics by counter-opposing available baseline characteristics versus log mortality RR, across different thresholds of HbA1c; and given single study arms' HbA1c thresholds versus logit mortality event rate. Study arms reporting "0 events" in both compared HbA1c thresholds were not considered for a subgroup meta-analysis. Single arms reporting "0 events" were not considered for meta-regression.

RESULTS

Study Selection and Participants

The Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram describing the study selection along with the reasons for exclusion is presented in Figure E1. After removal of reports not pertinent to the design of the current review, 30 observational studies that met inclusion criteria remained,[19-25,E1-E23] including a total of 34,650 patients. The selected articles were published between 2008 and 2020, and the number of patients for each trial ranged from 72 to 6415. Engoren and colleagues[E24] report long-term outcomes in a separate report. Of 30 studies, 21 compared 2 thresholds and 9 reported on more subgroups.

Tables E1 and E2 summarize the main characteristics and outcomes of the included studies. The mean age of the patients was 63.2 ± 3.2 years, and approximately 60% of cases had preoperative history of DM. CABG was the surgical procedure most frequently performed (94.9%), followed by valve surgery (3.3%). A summary of the risk of biases of included trial is reported in Table E3. Overall, quality assessment indicated no low-quality study.

Early Mortality

All 30 studies contributed to the analysis of early mortality. Visual inspection of the funnel plot for the primary end point showed a symmetrical distribution indicating no evidence of publication bias, and this was confirmed in Egger's test (Figure E2). Overall early mortality was 1.9% (656/34,650) (Table E2). The direction of the estimates in each glycemic level comparison subgroup favored lower HbA1c level, which reached significance in the subgroup comparing less than 5.5% versus more than 5.5%, with 1.06% (23/2177 patients) and 2.05% (102/4973 patients) corresponding early mortality rates (RR, 0.39, 95% CI, 0.18-0.84, $P = .02$, heterogeneity $P = .24$, $I^2 = 29\%$) (Figure 1). A "J-shaped" relationship was found between log RR of early mortality and HbA1c successive thresholds (Figure 2) (exponential function = coefficient 6.91 CIs [6.69-7.14], $P < .001$). The trend of reduction was present in the subgroup comparing less than 7.0% versus more than 7.0%, with 1.57% (248/15,644 patients) and 2.26% (209/9267 patients) dying in an early postoperative period (RR, 0.79, 95% CI, 0.59-1.05, $P = .10$, heterogeneity $P = .09$, $I^2 = 31\%$). Meta-regression analysis performed counter-opposing RR of early mortality against baseline characteristics of patients in the included studies (age, gender, diabetes, heart failure) in each threshold did not show the RR, being significantly influenced by variability of these characteristics in single studies. A trend toward lesser benefit with HbA1c less than 7.5% and HbA1c less than 8.0% was seen with increasing number of patients with a history of heart failure (Table E4). Restricting the analysis to the patients undergoing CABG (eg, excluding 2 studies[E7,E23] conducted in the setting of valve surgery exclusively) did not change the direction or magnitude of the estimates. As a further sensitivity analysis, a meta-regression of single study arms' HbA1c thresholds versus logit mortality event rate was performed; there was a significant linear relationship with lower baseline HbA1c levels and lower mortality rates (ßcoefficient = −1.175; $P = .025$).

Late Mortality

Eight studies[19,23,E4,E6,E11,E13,E15,E24] with 15,464 patients provided late mortality data. Mean (weighted) follow-up was 3.9 ± 1.4 years (range, 1.0-5.5 years) (Table E2). A lower HbA1c level resulted in reduced late mortality in every glycometabolic level comparison subgroup: less than 5.5% versus more than 5.5% (−44% rate reduction, $P = .09$), 6.0% versus more than 6.0% (−45% rate reduction, $P = .07$), less than 6.5% versus more than 6.5% (−41% rate reduction, $P = .01$), less than 7.0% versus more than 7.0% (−26% rate reduction, $P = .01$), less than 7.5% versus more than 7.5% (−25% rate reduction, $P = .01$), less than 8.0% versus more than 8.0% (−22% rate reduction, $P = .003$) (Figure 3).

Sternal Wound Infection

A total of 22 studies[19-25,E1-E3,E5,E7-E16,E22] enrolling 25,843 patients contributed to the analysis of sternal wound infections. The highest HbA1c subgroup comparisons were associated with the highest benefit of lower glycometabolic

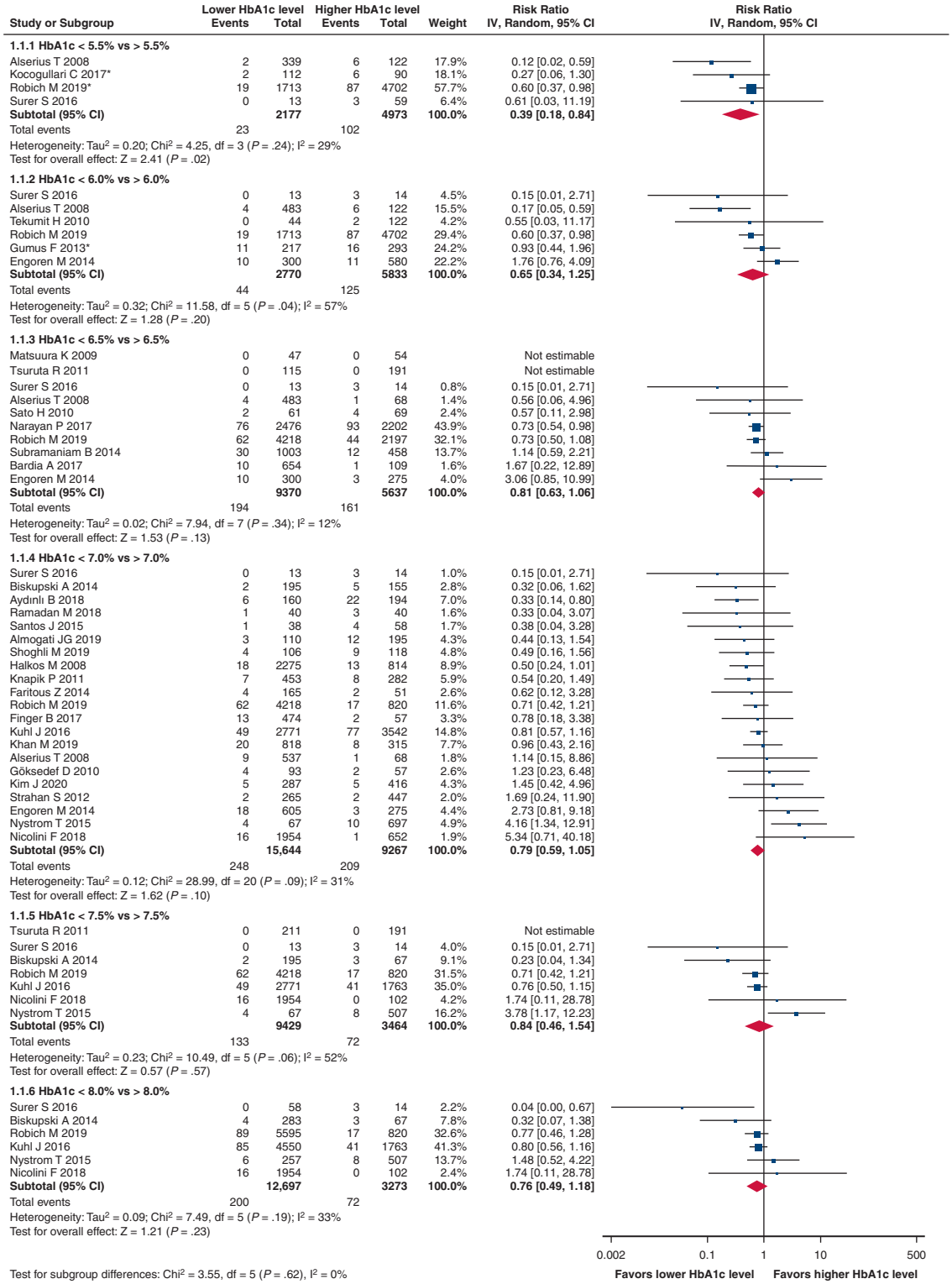

FIGURE 1. Stratified meta-analysis of lower versus higher HbA1c levels for the analysis of primary end point: early mortality. RRs are reported for each study and pooled within the respective subgroup. *Size of a square* corresponds to statistical weight of a study; *red diamonds* are indicative of effect estimate. *HbA1c*, Glycosylated hemoglobin; *IV*, inverse variance; *CI*, confidence interval. *Study was included in the threshold following approximation of achieved HbA1c level: Kocogulları C 2017: HbA1c 5.6% instead of 5.5%; Robich M 2019: HbA1c 5.7% instead of 5.5%; Gumus F 2013: HbA1c 5.9% instead of 6.0%.

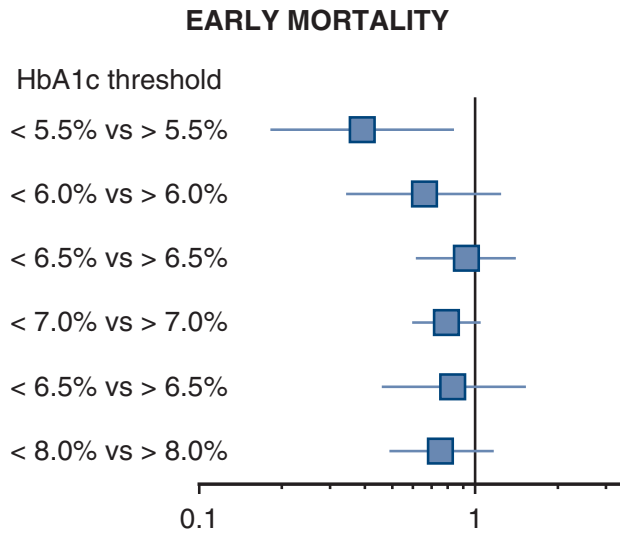

FIGURE 2. Reduction of risk for early mortality in patients with preoperative optimal glycemic control. *HbA1c*, Glycosylated hemoglobin.

level comparator, with a risk reduction of −77% (P <.0001, <8.0% vs >8.0%), −78% (P < .001, <7.5% vs >7.5%), −63% (P < .0001, <7.0% vs >7.0%), −52% (P < .0001, <6.5% vs >6.5%), −53% (P = .02, 6.0% vs >6.0%) (Figure 4).

Stroke/Transient Ischemic Attack

A total of 19 studies[20-25,E1,E3,E5,E7-E15,E18] with 24,451 patients provided data for the stroke/TIA analysis. Two subgroups, less than 7.0% versus more than 7.0% (RR, 0.53, 95% CI, 0.39-0.70, P < .0001, heterogeneity P = .78, I^2 = 0%) and less than 7.5% versus more than 7.5% (RR, 0.50, 95% CI, 0.32-0.80, P = .003, heterogeneity P = .67, I^2 = 0%), yielded the highest stroke/TIA. The statistically significant stroke/TIA reduction in the lower HbA1c group was also present in all remaining comparisons: less than 6.5% versus more than 6.5% (RR, 0.72, 95% CI, 0.53-0.97, P = .03, heterogeneity P = .36, I^2 = 9%) and less than 8.0% versus more than 8.0% (RR, 0.56, 95% CI, 0.36-0.87, P = .01, heterogeneity P = .84, I^2 = 0%) (Figure 5).

Acute Kidney Injury

A total of 21 studies[20-25,E1-E3,E5,E7-E15,E18,E20] with 24,869 patients provided data for the AKI analysis. The direction of the estimates in each glycemic level comparison subgroup favored lower HbA1c level, which reached a trend of reduction in the subgroup comparing less than 6.0% versus more than 6.0% (RR, 0.46, 95% CI, 0.18-1.15, P = .10, heterogeneity P = .005, I^2 = 81%). The subgroup less than 7.0% versus more than 7.0% yielded the lower AKI rate (RR, 0.65, 95% CI, 0.54-0.79, P < .0001, heterogeneity P = .10, I^2 = 35%). The statistically significant AKI reduction in the lower HbA1c group was also present in all remaining comparison thresholds: less than 6.5% versus more than 6.5% (RR, 0.77, 95% CI, 0.71-0.84, P <.0001, heterogeneity P = .58, I^2 = 0%), less than 7.5% versus more than 7.5% (RR, 0.73, 95% CI, 0.65-0.82, P < .0001, heterogeneity P = .74, I^2 = 0%), and less than 8.0% versus more than 8.0% (RR, 0.76, 95% CI, 0.68-0.85, P <.0001, heterogeneity P = .60, I^2 = 0%) (Figure 6).

Myocardial Infarction

Thirteen studies[19,20,22-25,E1-E3,E5,E7,E11,E18] with 9803 patients reported MI data. There were no statistically significant differences between lower and higher values of HbA1c in terms of MI (Figure E3), although there was a numeric reduction in the number of MIs in the subgroup comparison less than 7.0% versus more than 7.0%: 1.59% (64/4036) versus 2.21% (47/2122) (RR, 0.71, 95% CI, 0.44-1.15, P = .17, heterogeneity P = .30, I^2 = 16%).

Hospital Length of Stay

Thirteen studies[19-22,24,25,E8,E11,E14-E16,E21,E23] with 8092 patients contributed to the analysis of length of hospital stay, which was estimated at 9.5 ± 4.1 days in the entire cohort (Table E2). Lower levels of HbA1c were associated with a significantly reduced length of stay: MD −0.61 (95% CI, −1.23 to −0.00, P = .05, heterogeneity P = .45; I^2 = 0%) in 6.0% versus more than 6.0%, MD −0.92 (95% CI, −1.69, −0.15, P = .02, heterogeneity P = .50; I^2 = 0%) in less than 6.5% versus more than 6.5%, MD −0.81 (95% CI, −1.11, −0.51, P < .0001, heterogeneity P = .32; I^2 = 14%) in less than 7.0% versus more than 7.0% (Figure E4).

DISCUSSION

The incidence of insulin resistance and DM continues to increase and remains a tremendous threat to public health.[1] However, increased random blood glucose levels are not specific to diabetic subjects. Hyperglycemia may be encountered in surgical and critically ill nondiabetic patients.[E25] Multiple daily glucose measurements or continuous blood glucose monitoring can give more reliable information on the glycometabolic status but are not applicable to a general population.[10] In addition to glucose measurements, a variety of different approaches have been proposed over time to evaluate and monitoring glycometabolic status.[E26] HbA1c values reflect the 2- to 3-month average endogenous exposure to glucose, including postprandial spikes in the blood glucose, and have low intraindividual variability, particularly in persons without DM.[E27] Therefore, HbA1c is currently thought to be a solid marker of the long-term glycometabolic status both in patients with and without DM.[13]

Limited numbers of studies have investigated the relationship between preoperative glycemic control, assessed by glycated hemoglobin (HbA1c) levels, and surgical outcomes in patients undergoing cardiac operation. The current

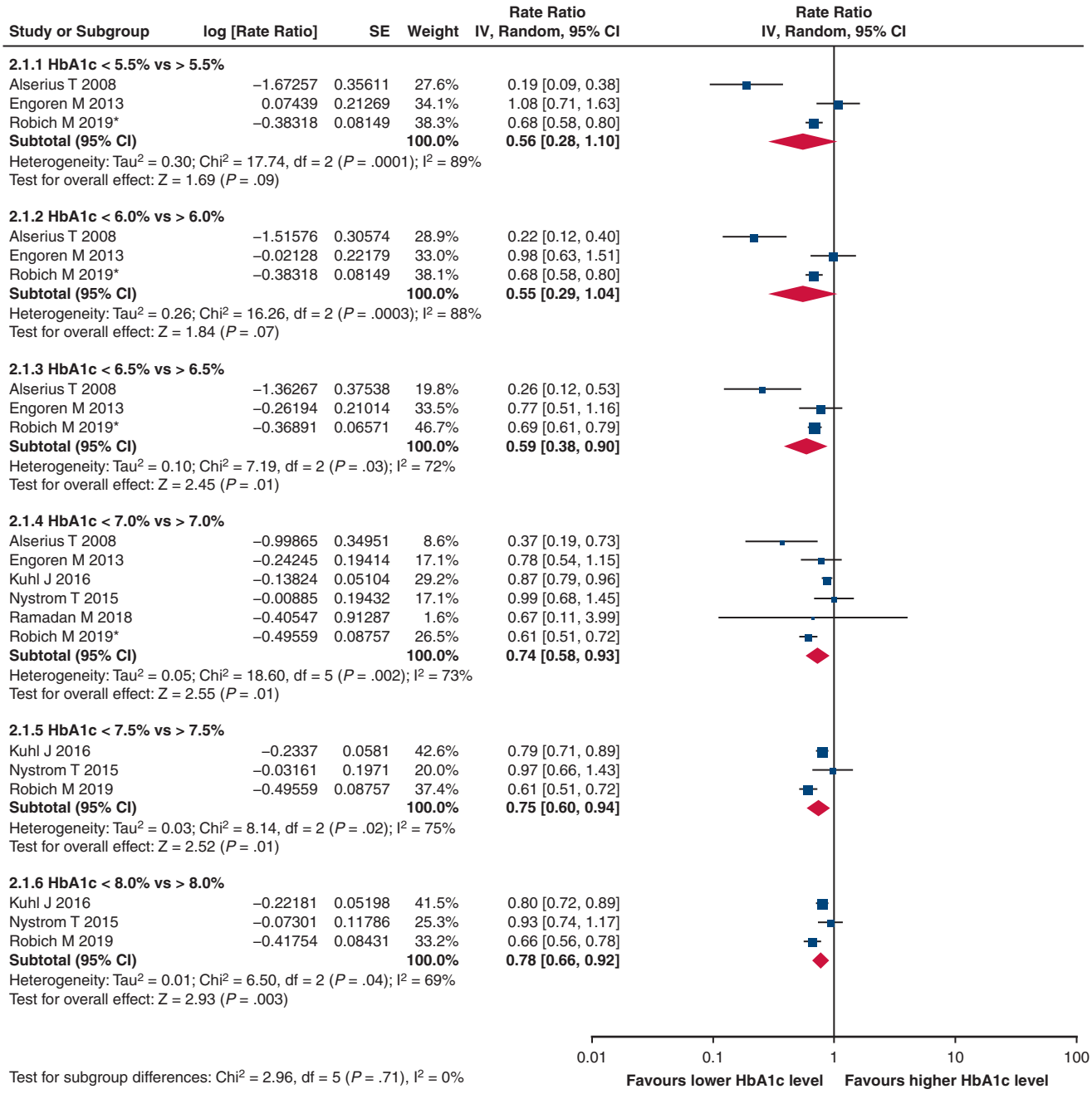

FIGURE 3. Stratified meta-analysis of lower versus higher HbA1c levels for the analysis of late mortality. RRs per person-years are reported for each study and pooled within the respective subgroup. Remaining information as in legend to Figure 1. *SE*, Standard error; *IV*, inverse variance; *CI*, confidence interval; *HbA1c*, glycosylated hemoglobin.

meta-analysis aimed to highlight the prognostic significance of preoperative glycometabolic status on long-term outcome in subjects undergoing a wide range of cardiac surgery procedures.

Our study provides a notable insight into the association between preoperative HbA1c level and morbidity, as well as mortality of patients undergoing cardiac surgeries. The degree of glycometabolic control affected the overall survival even in the early 30-day period. The highest benefit of the early mortality reduction was observed in the less than 5.0% versus more than 5.0% HbA1c level. Likewise, the late mortality had the lowest prevalence within the lowest HbA1c level comparison, which, driven by a higher number of events observed over longer period of time, reached statistical significance in every analyzed threshold, as resembled by the J-shaped mortality curve. To our knowledge, this is the first report to present results of even slightly elevated HbA1c levels, a nonprocedure-specific variable, that may affect a hard clinical outcome such as mortality at short-term follow-up.

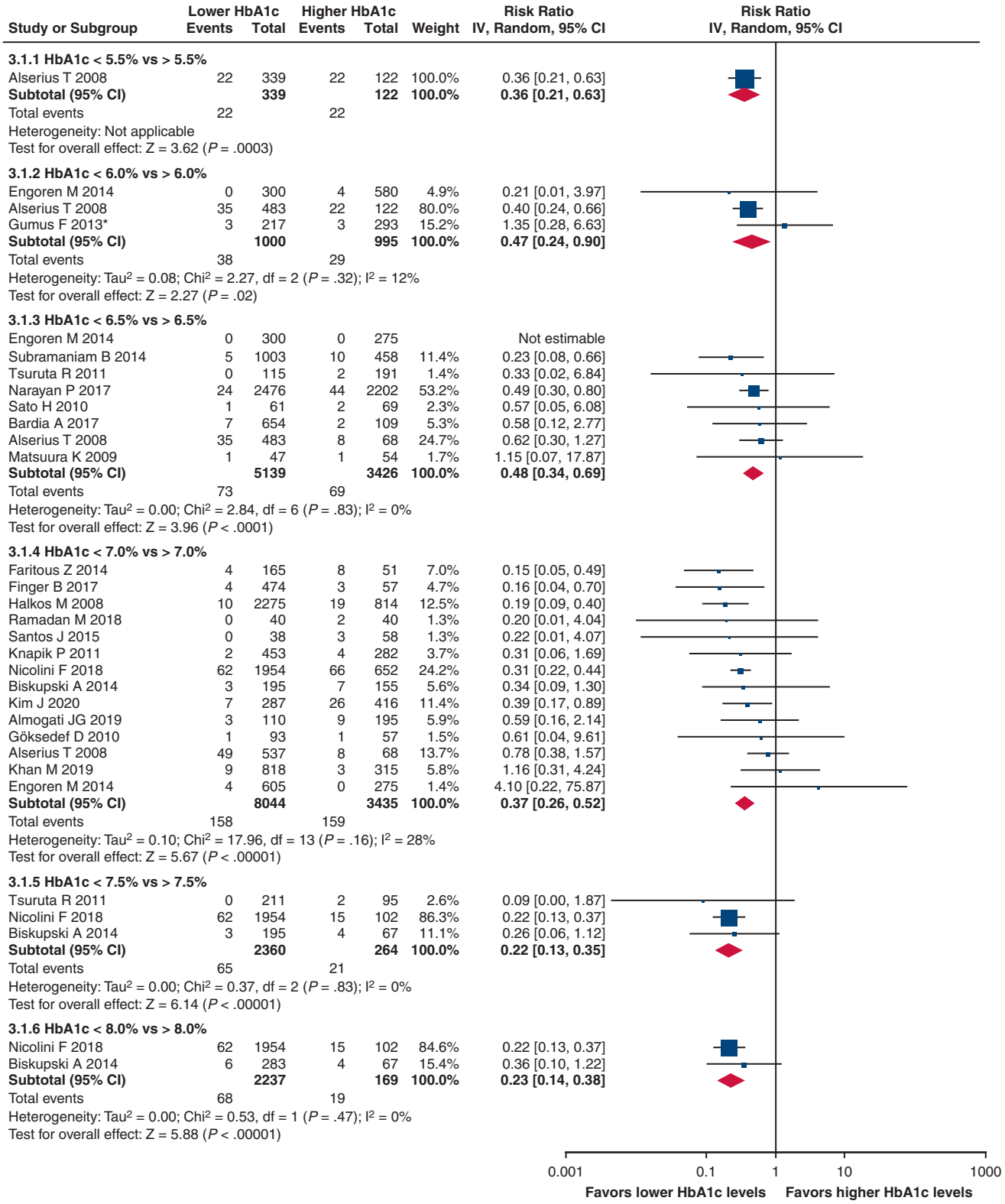

FIGURE 4. Stratified meta-analysis of lower versus higher HbA1c levels for the analysis of sternal wound infection. RRs are reported for each study and pooled within the respective subgroup. Remaining information as in legend to Figure 1. *HbA1c*, Glycosylated hemoglobin; *IV*, inverse variance; *CI*, confidence interval.

Independently of diabetic status, perioperative elevated levels of blood glucose have been linked with increases in morbidity and mortality, and prolonged hospitalization after surgery.[E28] Hyperglycemia-induced oxidative stress induces endothelial dysfunction that plays a central role in the pathogenesis of tissue and organ damage.[E29] Trials

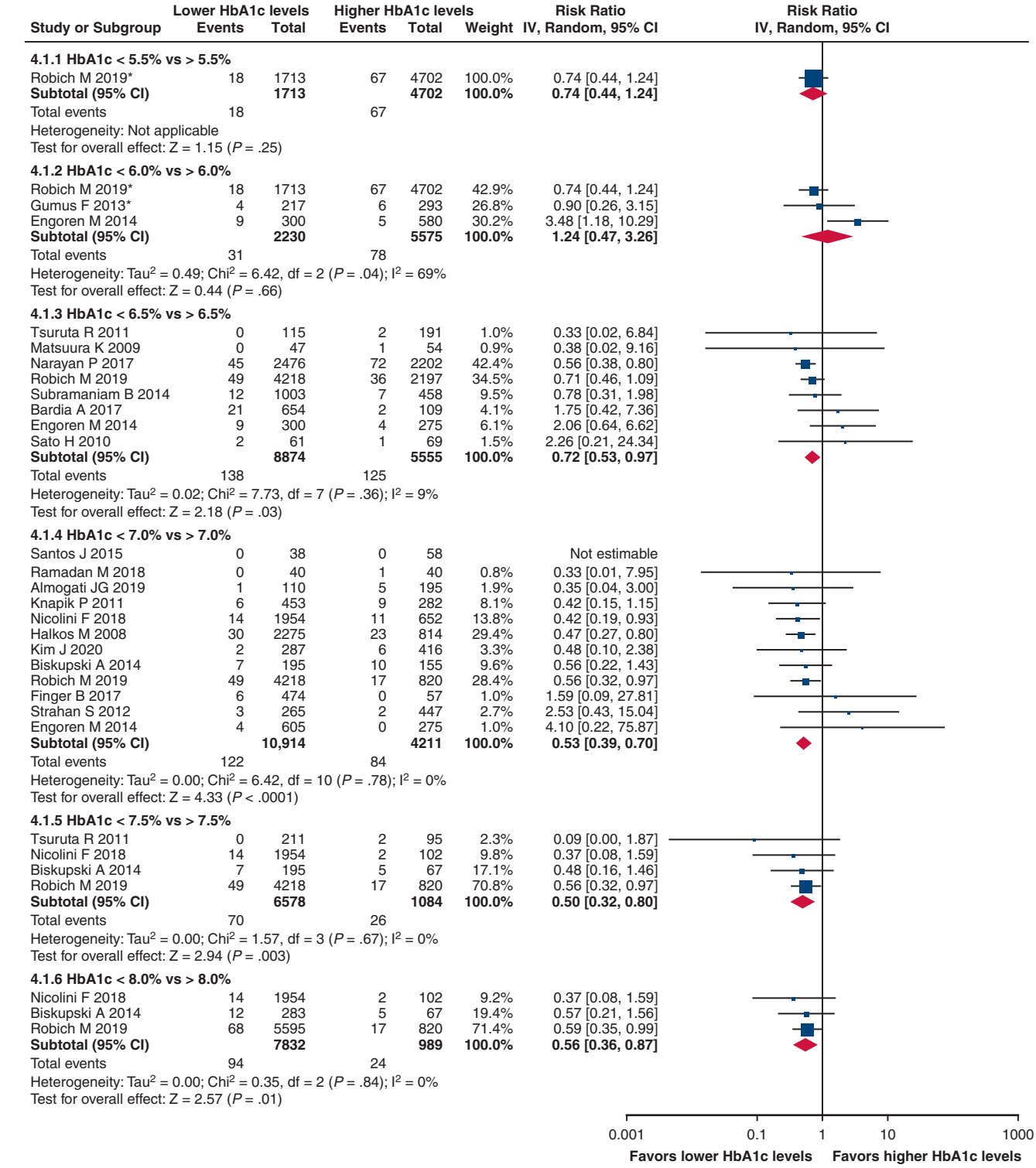

FIGURE 5. Stratified meta-analysis of lower versus higher HbA1c levels for the analysis of stroke or TIA. RRs are reported for each study and pooled within the respective subgroup. Remaining information as in legend to Figure 1. *HbA1c*, Glycosylated hemoglobin; *IV*, inverse variance; *CI*, confidence interval.

have clearly demonstrated that the risk of cardiovascular events and deaths can be reduced by intensive glucose control.[11,E30] Our findings suggest that altered relatively long-term glycometabolic status, regardless of a preexisting diagnosis of DM, is associated with an increased risk of postoperative mortality, AKI, neurologic complications, wound infection, and prolonged hospital length of stay in patients undergoing cardiac surgery.

Study or Subgroup	Lower HbA1c levels Events	Total	Higher HbA1c levels Events	Total	Weight	Risk Ratio IV, Random, 95% CI
5.1.1 HbA1c < 5.5% vs > 5.5%						
Kocogullari C 2017*	4	112	15	90	41.7%	0.21 [0.07, 0.62]
Robich M 2019*	344	1713	1166	4702	58.3%	0.81 [0.73, 0.90]
Subtotal (95% CI)		**1825**		**4792**	**100.0%**	**0.47 [0.13, 1.68]**
Total events	348		1181			
Heterogeneity: Tau² = 0.73; Chi² = 5.90, df = 1 (*P* = .02); I² = 83%						
Test for overall effect: Z = 1.17 (*P* = .24)						
5.1.2 HbA1c < 6.0% vs > 6.0%						
Gumus F 2013*	4	217	35	293	27.8%	0.15 [0.06, 0.43]
Engoren M 2014	6	300	20	580	30.0%	0.58 [0.24, 1.43]
Robich M 2019*	344	1713	1166	4702	42.2%	0.81 [0.73, 0.90]
Subtotal (95% CI)		**2230**		**5575**	**100.0%**	**0.46 [0.18, 1.15]**
Total events	354		1221			
Heterogeneity: Tau² = 0.51; Chi² = 10.51, df = 2 (*P* = .005); I² = 81%						
Test for overall effect: Z = 1.65 (*P* = .10)						
5.1.3 HbA1c < 6.5% vs > 6.5%						
Sato H 2010	1	61	3	69	0.1%	0.38 [0.04, 3.53]
Engoren M 2014	6	300	12	275	0.8%	0.46 [0.17, 1.20]
Narayan P 2017	73	2476	96	2202	7.9%	0.68 [0.50, 0.91]
Subramaniam B 2014	27	1003	17	458	2.0%	0.73 [0.40, 1.32]
Robich M 2019	908	4218	602	2197	88.5%	0.79 [0.72, 0.86]
Tsuruta R 2011	2	115	3	191	0.2%	1.11 [0.19, 6.53]
Bardia A 2017	22	654	3	109	0.5%	1.22 [0.37, 4.01]
Matsuura K 2009	3	47	0	54	0.1%	8.02 [0.42, 151.39]
Subtotal (95% CI)		**8874**		**5555**	**100.0%**	**0.77 [0.71, 0.84]**
Total events	1042		736			
Heterogeneity: Tau² = 0.00; Chi² = 5.62, df = 7 (*P* = .58); I² = 0%						
Test for overall effect: Z = 5.96 (*P* < .00001)						
5.1.4 HbA1c < 7.0% vs > 7.0%						
Santos J 2015	0	38	6	58	0.4%	0.12 [0.01, 2.01]
Ramadan M 2018	1	40	3	40	0.7%	0.33 [0.04, 3.07]
Halkos M 2008	40	2275	40	814	12.5%	0.36 [0.23, 0.55]
Biskupski A 2014	4	195	7	155	2.2%	0.45 [0.14, 1.52]
Kim J 2020	7	287	22	416	4.4%	0.46 [0.20, 1.07]
Knapik P 2011	3	453	4	282	1.5%	0.47 [0.11, 2.07]
Engoren M 2014	14	605	12	275	5.2%	0.53 [0.25, 1.13]
Faritous Z 2014	6	165	3	51	1.8%	0.62 [0.16, 2.38]
Robich M 2019	908	4218	242	820	32.4%	0.73 [0.65, 0.82]
Almogati JG 2019	5	110	12	195	3.1%	0.74 [0.27, 2.04]
Nicolini F 2018	381	1954	168	652	29.5%	0.76 [0.65, 0.89]
Strahan S 2012	4	265	8	447	2.3%	0.84 [0.26, 2.77]
Finger B 2017	67	474	5	57	4.1%	1.61 [0.68, 3.83]
Subtotal (95% CI)		**11,079**		**4262**	**100.0%**	**0.65 [0.54, 0.79]**
Total events	1440		532			
Heterogeneity: Tau² = 0.02; Chi² = 18.51, df = 12 (*P* = .10); I² = 35%						
Test for overall effect: Z = 4.49 (*P* < .00001)						
5.1.5 HbA1c < 7.5% vs > 7.5%						
Biskupski A 2014	4	195	4	67	0.7%	0.34 [0.09, 1.34]
Tsuruta R 2011	3	211	2	95	0.4%	0.68 [0.11, 3.98]
Robich M 2019	908	4218	242	820	88.1%	0.73 [0.65, 0.82]
Nicolini F 2018	381	1954	26	102	10.8%	0.76 [0.54, 1.08]
Subtotal (95% CI)		**6578**		**1084**	**100.0%**	**0.73 [0.65, 0.82]**
Total events	1296		274			
Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 3 (*P* = .74); I² = 0%						
Test for overall effect: Z = 5.48 (*P* < .00001)						
5.1.6 HbA1c < 8.0% vs > 8.0%						
Biskupski A 2014	7	283	4	67	0.8%	0.41 [0.12, 1.37]
Nicolini F 2018	381	1954	26	102	10.2%	0.76 [0.54, 1.08]
Robich M 2019	1268	5595	242	820	89.0%	0.77 [0.68, 0.86]
Subtotal (95% CI)		**7832**		**989**	**100.0%**	**0.76 [0.68, 0.85]**
Total events	1656		272			
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 2 (*P* = .60); I² = 0%						
Test for overall effect: Z = 4.82 (*P* < .00001)						

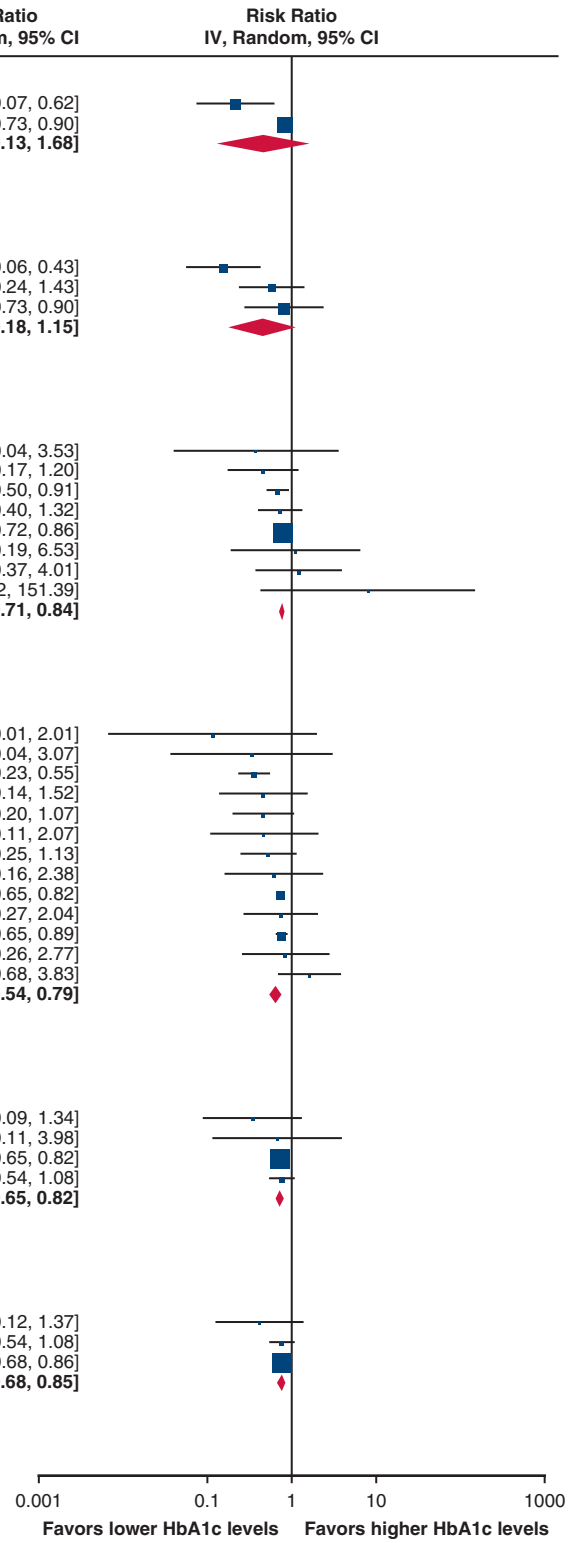

FIGURE 6. Stratified meta-analysis of lower versus higher HbA1c levels for the analysis of AKI. RRs are reported for each study and pooled within the respective subgroup. Remaining information as in legend to Figure 1. *HbA1c*, Glycosylated hemoglobin; *IV*, inverse variance; *CI*, confidence interval.

The highest rate of stroke/TIA and AKI was found in the threshold comparing 7.0% versus more than 7.0% of HbA1c, with 35% and circa 50% rate reduction in patients with lower glycemic level. Those results are in line with the recommendations of the American Diabetes Association emphasizing the need of achieving HbA1c levels less than 7%, for the reduction of diabetic-specific outcomes. Although the general association between wound infection

and diabetes is well established, and confirmed by our report, cerebrovascular outcomes are not specific for diabetic patients in cardiac surgery. Those findings emphasize the need to optimize hypoglycemic treatment for a long period of time before elective cardiac surgery to lower the risk of clinical end points, as well as the hospitalization length, which ultimately would translate to a total reduction in the treatment costs.

Although the association between HbA1c levels and perioperative MI was not statistically significant, a trend toward a higher risk of MI with higher HbA1c levels was observed, which is in accordance with a previous report.[E2] The results of the current study were consistent with those of current systematic reviews, namely, the preoperative HbA1c level had a statistically significant effect on the incidence of mortality in diabetic patients after cardiac surgery.[E31] However, a recent meta-analysis showed contrasting results,[E32] mainly because the authors included the percutaneous coronary intervention studies and the follow-up time for postoperative mortality varied greatly (ranging from before discharge to 7 years after surgery). Moreover, Wang and colleagues[E32] focused only on elective CABG surgery, ignoring the other cardiac surgical procedures.

The exact mechanisms underlying the correlation between higher HbA1c concentrations and worse clinical outcomes have not been adequately elucidated. Our results can be explained in several ways. First, higher HbA1c levels are commonly associated with metabolic syndrome whose components (obesity, dyslipidemias, hypertension, insulin resistance) increase the risk of worse surgical outcome.[E31,E33] Second, chronic hyperglycemia contributes to oxidative stress and endothelial damage, which can ultimately lead to organ dysfunction.[E29]

An increasing number of patients with a history of DM are presenting for valve surgery; thus, the effect of this disease on outcomes becomes important when discussing surgical options. Previous studies have indicated that DM had a negative impact on survival in patients undergoing valve replacement, particularly with regard to bioprosthesis.[E34,E35] On this basis, stricter glycemic control might be advisable in adults undergoing tissue valve implantation who have an exceedingly high risk of structural valve degeneration, such as diabetic and dialyzed subjects. However, because most reports included in the current review analyzed patients referred to CABG, a general conclusion cannot be drawn from this study. Therefore, whether adequate glucose control improved surgical outcomes in diabetic and nondiabetic adults undergoing valve operation must be demonstrated in dedicated prospective trials.

DM represents a significant toll on health budgets around the world, accounting for 5% to 20% of total healthcare expenditure in many countries.[E36] Both absolute costs and proportion of overall health budget for DM are set to increase in the future decades as prevalence increases; therefore, cost-effective treatment and prevention strategies will become increasingly important as resources become stretched.[E37] Preoperatively identifying an abnormally high HbA1c in patients with DM or prediabetes or not yet diagnosed diabetes helps direct attention to optimize glycemic control in patients with elevated HbA1c levels to minimizing the subsequent incidence of postoperative complications and reducing the costs of health care.[E38]

In contrast to preoperative impaired glycometabolic status, the impact of postoperative abnormal or appropriate glycemic control is unknown. Few studies have addressed such issues, although persistent hyperglycemic metabolic syndrome is expected to exert substantial influence on several aspects of postoperative surgical results, ranging from revascularization recurrence or tissue valve degeneration, endocarditis, or other adverse events. It is uncertain how a well-compensated or not well-compensated metabolic syndrome may affect patient well-being, implanted device or prosthetic function/integrity, or progression of the underlying disease. These aspects should represent a critical target for future investigation to assess the association between enhanced and optimal DM control versus long-term adverse event rates.

Study Limitations

Although the results from this meta-analysis raise the possibility that preoperative optimal glycometabolic status may confer some benefit to subjects undergoing cardiac surgery, there are a number of limitations that should be considered in the interpretation of our results. First, most of the included studies have a retrospective nature. Retrospective studies are subject to confounders and bias, possibly affecting the conclusive power of this meta-analysis. Second, critical information, such as type of DM, ejection fraction, coronary artery disease, timing of surgery, and comorbidities, which are potential confounders, was not reported in several studies, and this may limit the effect size of our findings. Third, we acknowledge the important methodological differences between studies: The varying proportion of diabetic and nondiabetic subjects may add to heterogeneity observed within single studies, in particular between less than 6.5% versus more than 6.5% and less than 7.0% versus more than 7.0% of HbA1c levels because these were cutoff values for DM diagnosis in some studies. On the other hand, inclusion by design both diabetic and nondiabetic populations confers the benefit of including patients with newly diagnosed DM in whom the effect of HbA1c lowering may be less pronounced. Last, we lacked information regarding the specific cause of death; therefore, only all-cause mortality was considered and investigated in the present meta-analysis.

CONCLUSIONS

The results of this study indicate that preoperative HbA1c levels may play an important role in the prognosis of

diabetic and nondiabetic patients undergoing cardiac surgery. Our meta-analysis, despite expected diversity for different outcomes likely due to its all-inclusive nature, suggests that HbA1c levels represent a continuous risk, ranging between 5.5% and 7.0%, with some variation in risk profiles at different levels of HbA1c. In particular, lower levels of preoperative HbA1c were associated with a lower risk of early and late mortality, as well as in the incidence of postoperative AKI, neurologic complications, and wound infection, compared with higher levels. Because preoperative HbA1c levels may universally predict possible high glucose-related complications of cardiac surgery, with lower values related to the better outcomes, it seems justified to recommend that all patients should undergo before the operation an HbA1c assay and a periodical control of metabolic compensation after surgery. Specifically, those patients with known diabetes should undergo cardiac surgery only after obtaining normalization or near normalization of HbA1c levels through optimization of their management. Moreover, the finding of not normal (>5.5.%) HbA1c levels in patients without a previous diagnosis of diabetes should prompt a presurgical metabolic workup to put in place adequate measures to obtain its normalization before the operation and during the follow-up.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: cardiac surgery, coronary artery bypass grafting, diabetes mellitus, glycosylated hemoglobin

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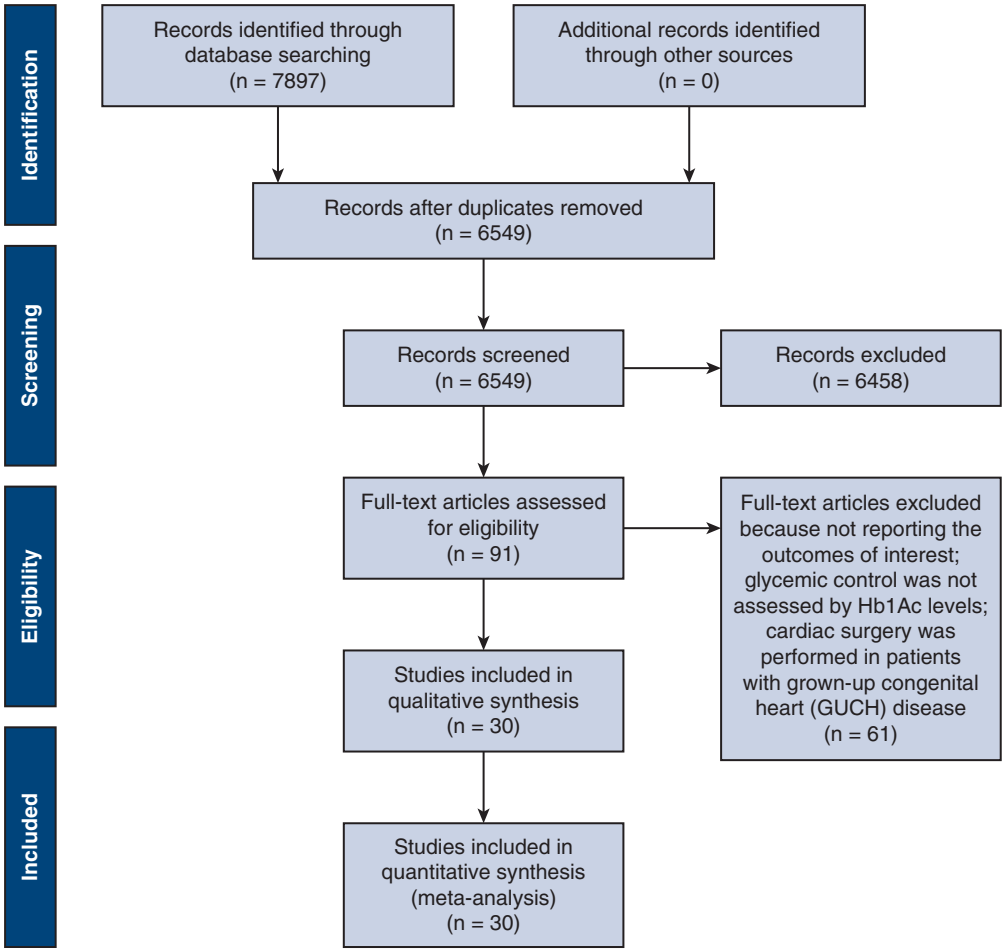

FIGURE E1. Preferred Reporting Items for Systematic Review and Meta-Analysis flow chart describing study selection process along with reasons for study exclusion. *HbA1c*, Glycosylated hemoglobin.

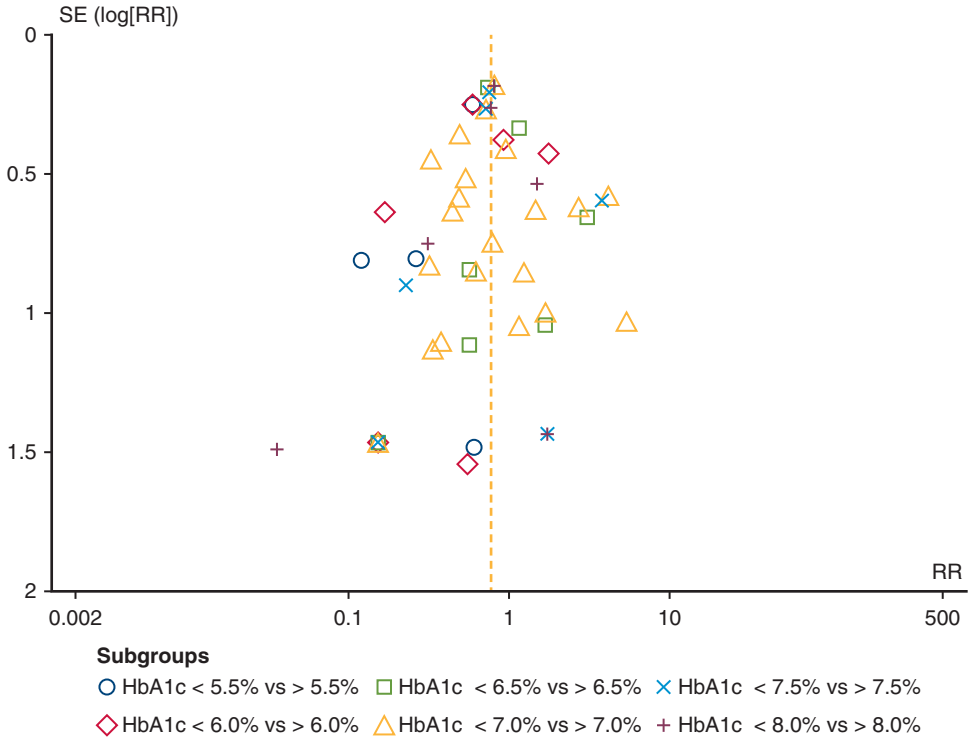

FIGURE E2. Publication bias analysis. Funnel plot. *SE*, Standard error; *RR*, risk ratio; *HbA1c*, glycosylated hemoglobin.

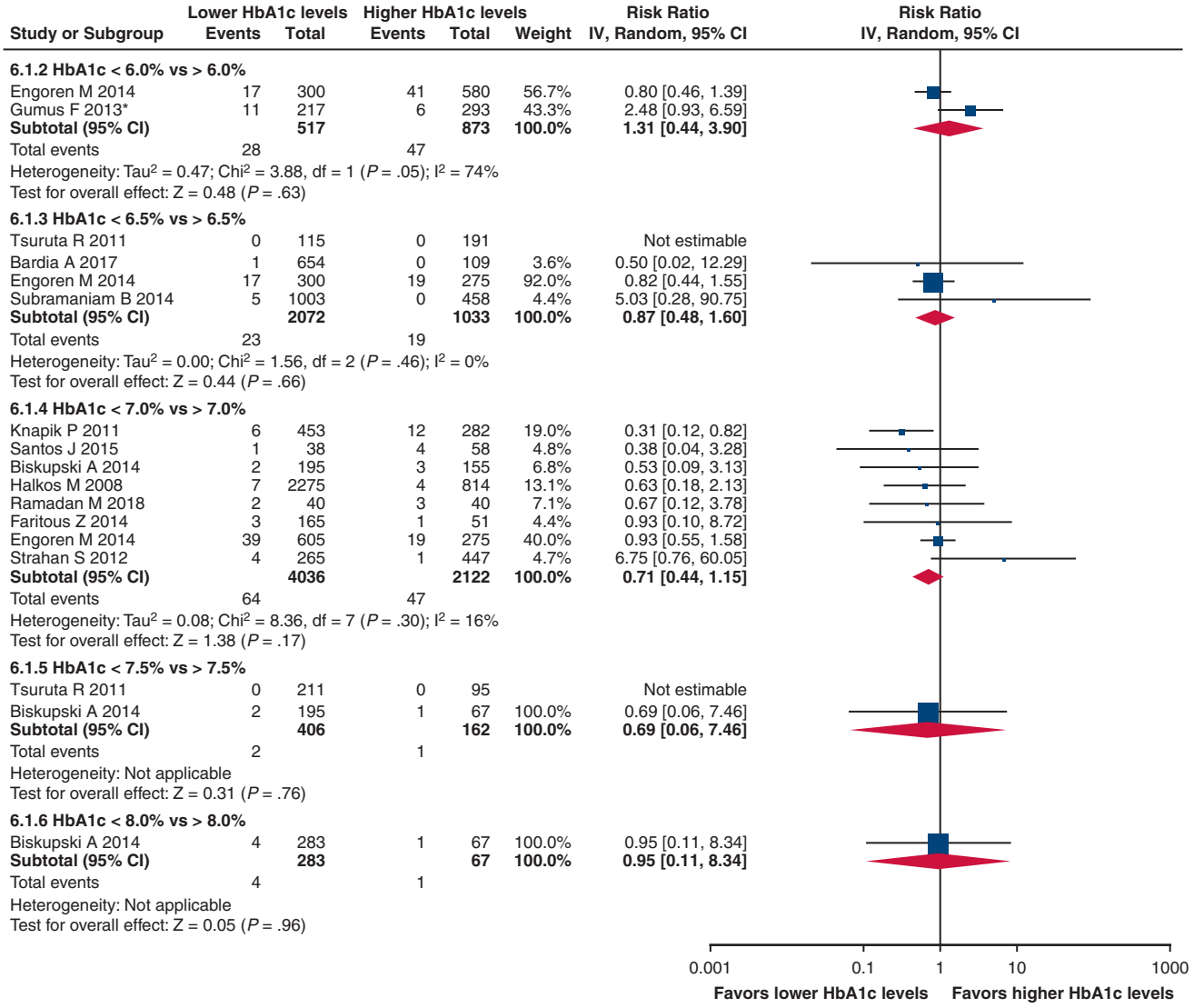

FIGURE E3. Meta-analysis of MI. *Size of a square* corresponds to statistical weight of a study; *black diamonds* are indicative of effect estimate. *HbA1c*, Glycosylated hemoglobin; *IV*, inverse variance; *CI*, confidence interval.

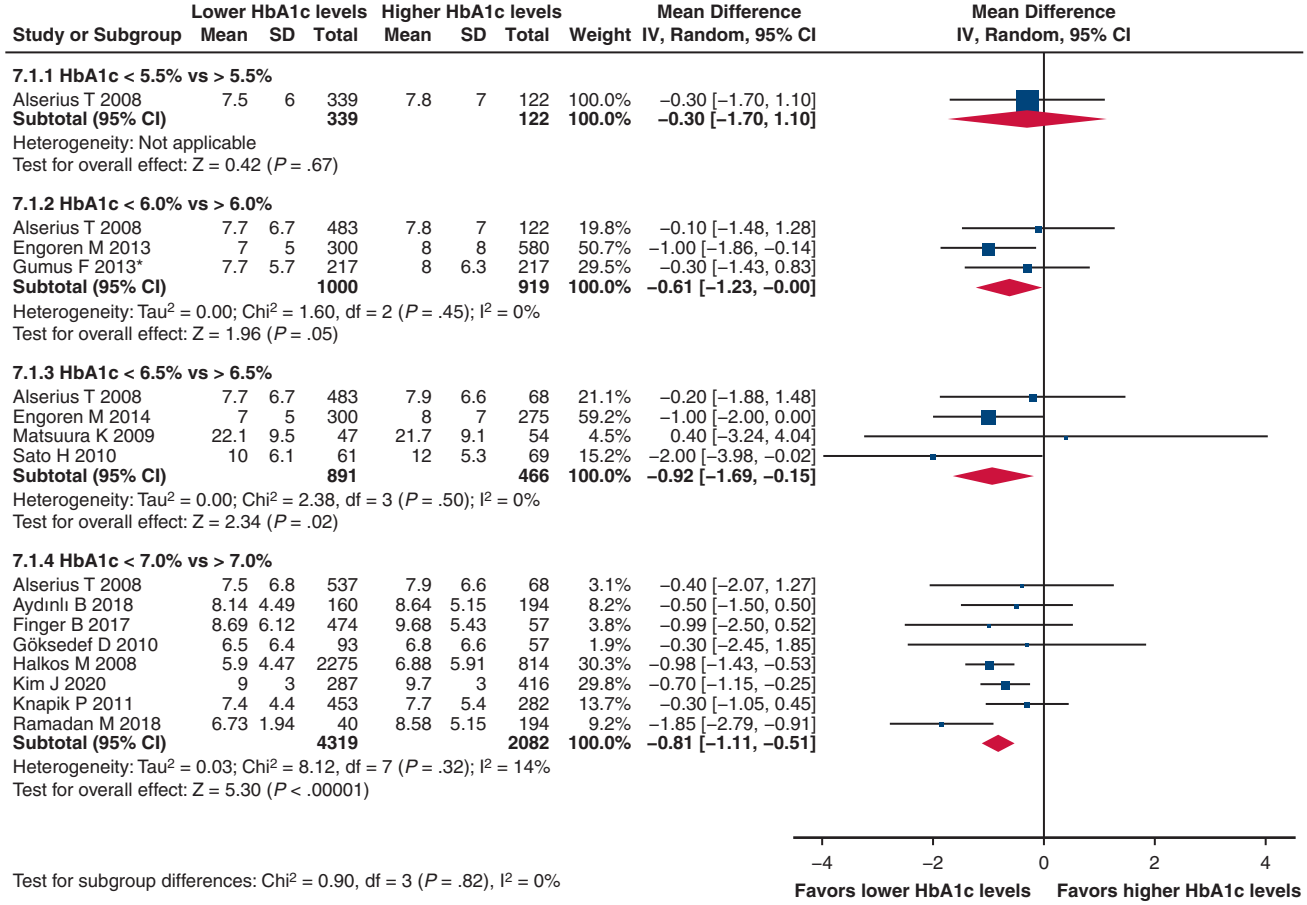

FIGURE E4. Meta-analysis of hospital length of stay. Size of a square corresponds to statistical weight of a study; black diamonds are indicative of effect estimate. *HbA1c*, Glycosylated hemoglobin; *SD*, standard deviation; *IV*, inverse variance; *CI*, confidence interval.

ADULT

TABLE E1. Patients' baseline characteristics

Author (Ref)	Year of publication	Patients (n)	Mean age (y)	Male (n)	DM (n)	HbA1c thresholds	Guidelines used, year	Type of cardiac operations (n)
Alserius T	2008	605	65	478 (79%)	161 (26.6%)	<5% vs 5% < 6% vs 6% < 7% vs ≥7%	Author choice	CABG = 605 (100%)
Halkos M	2008	3089	62.6	2243 (72.6%)	1240 (40.1%)	<7% vs ≥7%	ADA, 2005*	CABG = 3089 (100%)
Matsuura K	2009	101	65.5	80 (79.2%)	101 (100%)	<6.5% vs ≥6.5%	Author choice	CABG = 101 (100%)
Göksedef D	2010	150	61.7	106 (70.7%)	53 (35.3%)	<7% vs ≥7%	ADA, 2005*	CABG = 150 (100%)
Sato H	2010	130	66.9	91 (70%)	130 (100%)	<6.5% vs ≥6.5%	IEC report, 2009†	CABG = 78 (60%); valve = 24 (18.5%); CABG + valve = 28 (21.5%)
Tekumit H	2010	166	60.8	104 (62.6%)	54 (32.5%)	<6.1% vs ≥6.1%	Author choice	CABG = 166 (100%)
Knapik P	2011	735	64.7	487 (66.2%)	735 (100%)	≤7% vs > 7%	ADA, 2005*	CABG = 735 (100%)
Tsuruta R	2011	306	59.8	242 (79.1%)	306 (100%)	<6.5% vs 6.5% < 7.5% vs ≥7.5%	Author choice	CABG = 306 (100%)
Strahan S	2012	712	NA	NA	712 (100%)	<7% vs ≥7%	UK PDS‡	CABG = 712 (100%)
Gumus F	2013	510	60.6	382 (74.9%)	205 (40.2%)	≤5.9% vs > 5.9%	Author choice	CABG = 491 (96.3%); CABG + valve = 19 (3.7%)
Biskupski A	2014	350	65.6	239 (68.3%)	350 (100%)	<7% vs 7% <8% vs > 8%	Author choice	CABG = 267 (76.3%); valve = 19 (5.4%); CABG + valve = 64 (18.3%)
Engoren M	2014	880	64.7	640 (72.7%)	415 (47.1%)	<6% vs 6% < 6.9% vs ≥7%	Author choice	CABG = 880 (100%)
Faritous Z	2014	216	64	138 (63.9%)	76 (35.2%)	≤7% vs > 7%	Author choice	CABG = 216 (100%)
Subramaniam B	2014	1461	68	1,093 (74.8%)	562 (38.5%)	<6.5% vs ≥6.5%	Author choice	CABG = 1083 (74.1%); CABG + valve = 378 (25.9%)
Nyström T	2015	764	57	425 (55.6%)	764 (100%)	≤7% vs 7.1% < 8% vs 8.1% < 9% vs 9.1% <10% vs > 10%	Author choice	CABG = 764 (100%)
Santos J	2015	96	63.6	79 (82.3%)	96 (100%)	≤7% vs > 7%	ADA, 2001§	CABG = 96 (100%)
Kuhl J	2016	6313	68.4	4834 (76.6%)	6313 (100%)	≤7% vs 7.1% < 8% vs 8.1% < 9% vs 9.1% <10% vs > 10%	Author choice	CABG = 6313 (100%)
Surer S	2016	72	63.2	40 (55.5%)	72 (100%)	<5.5% vs 5.5% <8% vs > 8%	Author choice	CABG = 72 (100%)
Bardia A	2017	763	67	418 (54.8%)	145 (19%)	<6.5% vs ≥6.5%	Author choice	Valve = 763 (100%)
Finger B	2017	531	62.6	385 (72.5%)	182 (34.3%)	≤7% vs > 7%	ADA, 2015	CABG = 269 (50.6%); valve = 121 (22.8%); CABG + valve = 52 (9.8%); other = 89 (16.8%)
Kocogullari C	2017	202	61.6	162 (80.2%)	0 (0%)	<5.6% vs ≥5.6%	Author choice	CABG = 202 (100%)
Narayan P	2017	4678	58.8	4254 (90.9%)	3045 (65.1%)	<6.5% vs ≥6.5%	Author choice	CABG = 4678 (100%)
Aydinli B	2018	354	60.8	223 (63%)	354 (100%)	<7% vs ≥7%	Author choice	CABG = 354 (100%)
Nicolini F	2018	2606	67.5	2241 (86%)	942 (36.1%)	<7% vs 7% <9% vs > 9%	Author choice	CABG = 2606 (100%)
Ramadan M	2018	80	57.4	61 (76.2%)	80 (100%)	≤7% vs > 7%	ADA, 2006‖	CABG = 80 (100%)
Almogati JG	2019	305	59.1	250 (82%)	249 (81.6%)	<7% vs ≥7%	ADA, 2017	CABG = 305 (100%)

(Continued)

TABLE E1. Continued

Author (Ref)	Year of publication	Patients (n)	Mean age (y)	Male (n)	DM (n)	HbA1c thresholds	Guidelines used, year	Type of cardiac operations (n)
Khan M	2019	1133	65	780 (68.8%)	545 (48.1%)	≤7% vs > 7%	Author choice	CABG = 1133 (100%)
Robich M	2019	6415	65.6	4965 (77.4%)	2674 (41.7%)	<5.7% vs 5.7% < 6.4% vs 6.5% <8% vs > 8%	ADA categories	CABG = 6415 (100%)
Shoghli M	2019	224	59.1	71 (31.7%)	224 (100%)	<7% vs ≥7%	ADA, 2014¶	Valve = 224 (100%)
Kim J	2020	703	65.8	499 (71%)	703 (100%)	<7% vs ≥7%	ADA, 2018#	CABG = 703 (100%)
Total		34,650	63.2 ± 3.2	26,010 (76.6%)	21,488 (62%)			CABG = 32,869; valve = 1151; CABG + valve = 541; other = 89

Data are shown as number (%) or mean value ± standard deviation. *DM*, Diabetes mellitus; *HbA1c*, glycosylated hemoglobin; *CABG*, coronary artery bypass grafting; *ADA*, American Diabetes Association; *IEC*, International Expert Committee; *NA*, not available; *UK PDS*, United Kingdom Prospective Diabetes Study. *American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2005;28(Suppl 1):4-36. †American Diabetes Association. Standards of medical care for patients with diabetes mellitus: Clinical practice recommendations 2001. *Diabetes Care*. 2001;24:(Suppl 1):S33-43. ‡The ACE/ADA Task Force on Inpatient Diabetes. American College of Endocrinology and American Diabetes Association Consensus Statement on inpatient diabetes and glycemic control. *Diabetes Care*. 2006;29:1955-62. §American Diabetes Association. Standards of medical care in diabetes–2014. *Diabetes Care*. 2014;37(Suppl 1):S14-80. ‖American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018;41(Suppl 1):S55-S64. ¶2009 International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care*. 32:1327-34. #UKPDS: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-53.

TABLE E2. Postoperative complications and outcomes

Author (Ref)	Early mortality (n)	Mean follow-up (y)*	Late mortality (n)	Sternal wound infection (n)	Stroke/TIA (n)	AKI (n)	MI (n)	Length of hospital stay (d)
Alserius T	10 (1.6%)	3.5	33 (5.4%)	59 (9.7%)	NA	NA	86 (14.2%)	7.7
Halkos M	31 (1%)	NA	NA	29 (0.9%)	53 (1.7%)	80 (2.6%)	11 (0.4%)	6.2
Matsuura K	0	2.4	0	2 (2%)	1 (1%)	3 (3%)	NA	21.9
Göksedef D	6 (4%)	NA	NA	2 (1.3%)	NA	NA	NA	6.6
Sato H	6 (4.6%)	NA	NA	16 (12.3%)	3 (2.3%)	4 (3%)	NA	9.6
Tekumit H	2 (1.2%)	NA	NA	NA	NA	NA	NA	NA
Knapik P	15 (2%)	NA	NA	6 (0.8%)	15 (2%)	7 (0.9%)	18 (2.4%)	7.5
Tsuruta R	0	3.6	19 (6.2%)	2 (0.6%)	2 (0.6%)	5 (1.6%)	0	NA
Strahan S	4 (0.6%)	NA	NA	NA	5 (0.7%)	12 (1.7%)	5 (0.7%)	NA
Gumus F	27 (5.3%)	NA	NA	6 (1.2%)	26 (5.1%)	39 (7.6%)	17 (3.3)	8.9
Biskupski A	7 (2%)	NA	NA	10 (2.8%)	17 (4.8%)	11 (3.1%)	5 (1.4%)	NA
Engoren M	19 (2.1%)	2.2†	122† (12.4%)	4 (0.4%)	14 (1.5%)	26 (2.7%)	58 (6%)	7.7
Faritous Z	6 (2.8%)	NA	NA	12 (5.5%)	NA	9 (4.2%)	4 (1.8%)	NA
Subramaniam B	42 (2.9%)	NA	NA	15 (1%)	19 (1.3%)	44 (3%)	5 (0.3%)	NA
Nyström T	14 (1.8%)	4.7	179 (23.4%)	NA	NA	NA	NA	NA
Santos J	5 (5.2%)	NA	NA	3 (3.1%)	0	6 (6.2%)	5 (5.2%)	NA
Kuhl J	126 (2%)	5.5	1630 (25.8%)	NA	NA	NA	NA	NA
Surer S	3 (4.2%)	NA	NA	NA	NA	NA	NA	NA
Bardia A	11 (1.4%)	NA	NA	9 (1.2%)	23 (3%)	25 (3.3%)	1 (0.1%)	NA
Finger B	15 (2.8%)	NA	NA	7 (1.3%)	6 (1.1%)	72 (13.5%)	NA	8.8
Kocogullari C	8 (4%)	NA	NA	NA	NA	19 (9.4%)	NA	NA
Narayan P	169 (3.6%)	NA	NA	106 (2.3%)	117 (2.5%)	169 (3.6%)	NA	NA
Aydinli B	28 (7.9%)	NA	NA	NA	NA	NA	NA	8.4
Nicolini F	17 (0.6%)	NA	NA	177 (6.8%)	25 (1%)	549 (21%)	NA	NA
Ramadan M	4 (5%)	1	5 (6.2%)	17 (21.2%)	2 (2.5%)	4 (5%)	5 (6.2%)	7.6
Almogati JG	15 (4.9%)	NA	NA	12 (3.9%)	6 (2%)	17 (5.6%)	NA	NA
Khan M	28 (2.5%)	NA	NA	12 (1.1%)	NA	NA	NA	NA
Robich M	15 (0.2%)	2.6	946 (14.7%)	12 (0.2%)	6 (0.1%)	16 (0.3%)	NA	NA
Shoghli M	13 (5.8%)	NA	NA	NA	NA	NA	NA	13.4
Kim J	10 (1.4%)	NA	NA	33 (4.7%)	8 (1.1%)	29 (4.1%)	NA	9
Total	656 (1.9%)	3.9 ± 1.4	2934 (18.8%)	551 (2.1%)	348 (1.4%)	1146 (4.6%)	220 (2.2%)	9.5 ± 4.1

Data are shown as number (%) or mean value ± standard deviation. *TIA*, Transient ischemic attack; *AKI*, acute kidney injury; *MI*, myocardial infarction; *NA*, not available. *Weighted mean follow-up. †Engoren M, Schwann TA, Arslanian-Engoren C, Maile M, Habib RH. U-shape association between hemoglobin A1c and late mortality in patients with heart failure after cardiac surgery. *Am J Cardiol*. 2013;111:1209-13.

TABLE E3. Quality scoring for included papers using the Quality In Prognosis Studies tool

Author	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Alserius T	low	low	low	low	moderate	low
Biskupski A	low	low	low	low	moderate	moderate
Faritous Z	low	low	low	low	moderate	low
Finger B	low	low	low	low	moderate	low
Gumus F	low	low	low	low	low	low
Halkos M	moderate	low	low	moderate	low	low
Kim J	low	low	low	low	moderate	low
Knapik P	low	low	low	low	moderate	low
Kuhl J	moderate	low	low	low	moderate	low
Narayan P	moderate	low	low	low	moderate	low
Nicolini F	low	low	low	low	moderate	low
Nyström T	low	low	low	low	moderate	low
Ramadan M	moderate	low	low	low	high	moderate
Robich MP	low	low	moderate	moderate	moderate	low
Santos J	moderate	low	low	low	moderate	low
Sato H	low	low	moderate	moderate	moderate	low
Subramaniam B	moderate	low	low	low	high	moderate
Bardia A	low	moderate	low	low	low	low
Tsuruta R	moderate	low	low	moderate	low	low
Engoren M	lode	low	low	low	moderate	moderate
Almogati JG	low	moderate	low	low	high	moderate
Matsuura K	low	low	low	low	low	low
Göksedef D	moderate	low	moderate	moderate	moderate	moderate
Tekumit H	moderate	low	low	low	low	low
Strahan S	low	low	low	moderate	high	low
Surer S	low	low	low	moderate	low	low
Kocogullari C	low	low	low	low	low	low
Aydinli B	low	low	low	low	low	low
Khan M	low	low	low	low	low	low
Shoghli M	moderate	moderate	moderate	moderate	moderate	low

Review authors' judgments about each risk of bias item for each included study.

TABLE E4. Meta-regression of primary end point against baseline variables

	Age (mean)		Male (%)		DM (%)	
	β-coefficient	*P*	β-coefficient	*P*	β-coefficient	*P*
Early mortality						
HbA1c <5.5% vs >5.5%	0.105	.724	−3.657	.610	1.459	.388
HbA1c <6.0% vs >6.0%	−0.117	.558	−4.317	.351	−1.134	.638
HbA1c <6.5% vs >6.5%	0.032	.473	−1.685	.243	−1.112	.136
HbA1c <7.0% vs >7.0%	0.016	.745	0.537	.708	−0.421	.434
HbA1c <7.5% vs >7.5%	−0.129	.074	−3.191	.340	−0.173	.914
HbA1c <8.0% vs >8.0%	−0.040	.563	0.714	.814	−0.495	.677

DM, Diabetes mellitus; *HbA1c*, glycosylated hemoglobin.