Effect of A1C and Glucose on Postoperative Mortality in Noncardiac and Cardiac Surgeries

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Hemoglobin A_{1c} (A1C) is used in assessment of patients for elective surgeries because hyperglycemia increases risk of adverse events. However, the interplay of A1C, glucose, and surgical outcomes remains unclarified, with often only two of these three factors considered simultaneously. We assessed the association of preoperative A1C with perioperative glucose control and their relationship with 30-day mortality.

RESEARCH DESIGN AND METHODS

Retrospective analysis on 431,480 surgeries within the Duke University Health System determined the association of preoperative A1C with perioperative glucose (averaged over the first 3 postoperative days) and 30-day mortality among 6,684 noncardiac and 6,393 cardiac surgeries with A1C and glucose measurements. A generalized additive model was used, enabling nonlinear relationships.

RESULTS

A1C and glucose were strongly associated. Glucose and mortality were positively associated for noncardiac cases: 1.0% mortality at mean glucose of 100 mg/dL and 1.6% at mean glucose of 200 mg/dL. For cardiac procedures, there was a striking U-shaped relationship between glucose and mortality, ranging from 4.5% at 100 mg/dL to a nadir of 1.5% at 140 mg/dL and rising again to 6.9% at 200 mg/dL. A1C and 30-day mortality were not associated when controlling for glucose in noncardiac or cardiac procedures.

CONCLUSIONS

Although A1C is positively associated with perioperative glucose, it is not associated with increased 30-day mortality after controlling for glucose. Perioperative glucose predicts 30-day mortality, linearly in noncardiac and nonlinearly in cardiac procedures. This confirms that perioperative glucose control is related to surgical outcomes but that A1C, reflecting antecedent glycemia, is a less useful predictor.

Hyperglycemia in the perioperative period is associated with adverse outcomes. The relationship between hyperglycemia and stress is well established, with higher rates of *1*) infection, *2*) delayed wound healing, *3*) neurologic injuries, and *4*) postoperative mortality (1). Increased insulin resistance induced by surgical stress and nociceptive signals during surgery are significant contributing factors (2,3). Gandhi et al. (4) found a 30% increase in rate of adverse postoperative events for every 20-mg/dL increase in intraoperative glucose level. Attempts to study the problem are frustrated by the fact that the definition of intraoperative hyperglycemia has been highly variable in both range and format (5).

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Hemoglobin A_{1c} (A1C) level gives an indirect measurement of how effectively an individual's blood glucose is controlled (6,7) and broadly predicts serum glucose (8). It is therefore often used to determine if a patient should be allowed to proceed with elective surgical procedures (9), even though its relation with poor postsurgical outcomes is less clear (6,10–13). Subramaniam et al. (14) contend that glycemic variability with elevated preoperative A1C predicts adverse outcomes in surgery, and indeed, glycemic variability does appear detrimental (15,16). Conversely, Ambiru et al. (17) find that A1C is not an independent predictor of infection when jointly analyzed with blood glucose level. Interestingly, both high and low A1C levels are associated with poor outcomes following surgery (18–20), suggesting that the relationship follows some nonlinear shape such as a parabola.

Despite numerous studies into the effect of A1C and hyperglycemia on postoperative outcomes (21,22), most consider hyperglycemia alone (1,23–26) or A1C alone (13,20,27). When studied together, they are most often not in a multivariable analysis (28,29) in which one can assess the effect of an indicator while controlling for another. Such analysis is pertinent when considering A1C and glucose because they are correlated. A thorough understanding of the interplay of preoperative A1C, perioperative glucose, and postoperative outcomes should inform the practice of A1C screening for elective surgery. Therefore, we investigate the association of A1C with postoperative mortality while controlling for perioperative glucose level. We used a large, single-center database including a wide variety of surgical procedures to examine these relationships. Patients undergoing cardiac and noncardiac procedures were analyzed separately.

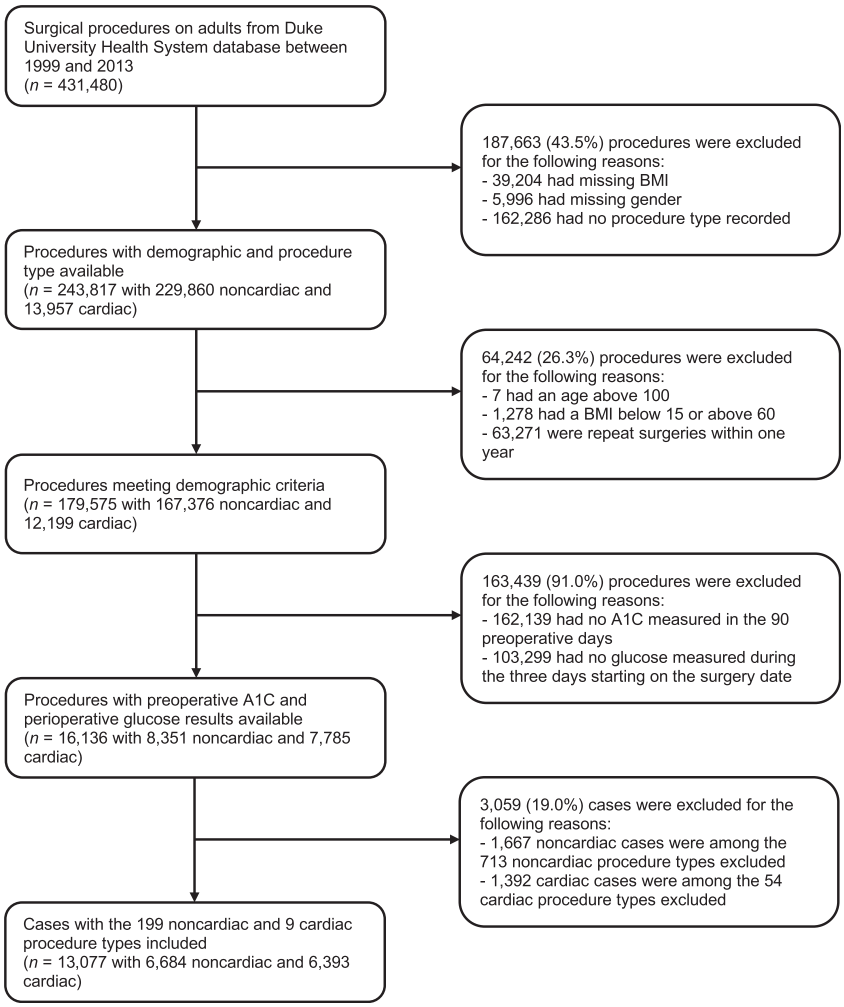

Figure 1—Case inclusion flow chart. Visual representation of how the 6,684 noncardiac and 6,393 cardiac cases analyzed were selected from the 431,480 surgical procedures available.

RESEARCH DESIGN AND METHODS

Data Description

Following institutional review board approval, de-identified data from 246,650 patients aged ≥18 years who underwent a total of 431,480 surgical procedures at Duke University Health System from 1999 through 2013 were obtained from a database of electronic medical records for retrospective analysis. Figure 1 describes the selection of the final 13,077 procedures.

The primary clinical outcomes were average perioperative blood glucose level and 30-day postoperative mortality. Average perioperative blood glucose level was computed as the mean of glucose measurements from the day of surgery until postoperative day 3. Using the median postoperative glucose instead to obviate the effect of outlier values does not materially change our findings. Thirty-day postoperative mortality was defined to occur whenever the postoperative status in the enterprise data warehouse was any option other than "alive" with a date within 30 days of surgery. Statuses other than "alive" were all labels corresponding to death such as "presumed dead" or "expired at Duke." Analogously, we considered 3-year and time-unlimited mortality based on medical records up to 2015.

We chose mortality as the measure of adverse postoperative outcome because it was, unlike other outcomes, reliably captured in the data. Our large database allowed the use of mortality, whereas smaller studies often lack statistical power to get results for such a rare outcome. As an outcome variable, mortality is very informative. Most interventions in medicine are focused on delaying mortality, and it has virtually no diagnostic error, unlike other outcomes. For instance, length of stay is more subjective as it is affected by many nonphysiological determinates including bed availability, transportation, efficiency of the discharge process, and variability in human decision-making.

The database did not contain reliable information on important confounders of glycemia or mortality such as comorbidities. To reduce confounding within these confines, the analysis controlled for type of procedure as provided by primary ICD-9 procedure codes. There were 680 noncardiac and 61 cardiac distinct ICD-9 codes present. To minimize the number of distinct types of surgery in the analysis, only the most common ICD-9 codes were included, comprising distinct ICD-9 codes for 199 noncardiac and 9 cardiac procedures and accounting for 80% of the total number of operations. Age, BMI, and sex served as additional controls. Surgeries were grouped as noncardiac and cardiac for analysis because of the prevalence of cardiopulmonary bypass and insulin use in cardiac surgeries.

Diabetes is an important confounder of both preoperative A1C and perioperative glucose. Unfortunately, our data captured this via ICD coding with an implausibly low diagnosis rate. Therefore, we did not include it in our main analysis. Results for the subset with a diabetes diagnosis are mentioned and provided in the Supplementary Data.

The primary independent variable in the analysis was preoperative A1C, measured closest to but not >90 days prior to the day of surgery. Eliminating cases lacking A1C measurements within 90 days of surgery or glucose values in the 3 days starting with the surgery date left 6,684 noncardiac and 6,393 cardiac procedures; missing A1C measurements were the most common cause of culling cases (Fig. 1). During the period examined, measurement of A1C was not used as a standard method for screening patients without diabetes for surgery. Supplementary Fig. 1 shows that the A1C measurements were closer to the surgery for cardiac than for noncardiac procedures. Table 1 shows summary statistics for various data subsets.

Table 1—Demographic and clinical characteristics

Characteristic	Mean or *n* (%)	SD	Quartiles Q1	Quartiles Median	Quartiles Q3
Data set: 167,376 noncardiac procedures not constrained by having preoperative A1C and perioperative glucose measured or by procedure type					
Age (years)	53	18	39	55	67
BMI	29	6.6	24	28	32
30-day postoperative mortality	1,456 (0.9%)				
Female	96,873 (58%)				
Data set: 6,684 noncardiac procedures constrained by having preoperative A1C and perioperative glucose measured and being among 199 types considered					
Age (years)	60	15	50	62	71
BMI	32	7.7	26	30	36
30-day postoperative mortality	156 (2.3%)				
Female	3,518 (53%)				
Average perioperative glucose (mg/dL)	149	42	118	142	172
No. of perioperative glucose measurements	11	11	2	8	15
A1C (%|mmol/mol)	7.1|54	1.7|19	5.9|41	6.6|49	7.8|62
Data set: 12,199 cardiac procedures not constrained by having preoperative A1C and perioperative glucose measured or by procedure type					
Age	62	14	54	63	72
BMI	29	6.0	25	28	32
30-day postoperative mortality	273 (2.2%)				
Female	4,557 (37%)				
Data set: 6,393 cardiac procedures constrained by having preoperative A1C and perioperative glucose measured and being among 9 types considered					
Age	64	12	56	65	73
BMI	29	6.0	25	28	32
30-day postoperative mortality	116 (1.8%)				
Female	2,257 (35%)				
Average perioperative glucose (mg/dL)	146	19	134	145	156
No. of perioperative glucose measurements	32	13	24	33	42
A1C (%|mmol/mol)	6.4|46	1.4|15	5.6|38	6.0|42	6.7|50

Summary statistics of demographic and clinical characteristics for the cardiac and noncardiac sets of surgeries not constrained and constrained by having both preoperative A1C and perioperative glucose measured and by being one of the procedure types considered.

Statistical Analysis

Previous studies (18,19) suggest a nonlinear relationship between A1C and mortality. Generalized additive models (30), a type of multivariable regression, allow for such nonlinearity. We include procedure type as a random effect to capture the correlation between similar cases while mitigating biases due to differences between procedure types. Generalized additive models with random effects are referred to as generalized additive mixed-effects models. We use such models to estimate the relation between preoperative A1C and both average perioperative glucose and postoperative mortality while controlling for age, BMI, sex, procedure type, and, for mortality, average perioperative glucose. The results when not controlling for procedure type are similar to those presented in this study with all conclusions being the same.

Generalized additive models were fit using R version 3.2.3 with the package "mgcv" version 1.8–9. An identity link with Gaussian errors was used for average perioperative glucose, whereas a logistic-binomial link was used for mortality. All continuous predictors were treated as having potentially nonlinear effects. Note that our analysis did not formally test for differences between noncardiac and cardiac procedures.

RESULTS

Average Perioperative Blood Glucose Level

Figure 2 shows the association between average perioperative glucose and A1C from the generalized additive model. There is a significant, positive, nonlinear relationship between A1C and average perioperative glucose ($P < 0.001$). The relationship is virtually linear between an A1C of 6% (42 mmol/mol) and 7.5% (59 mmol/mol), with flattening of the curve at higher A1C values. The relationship of A1C with average glucose is stronger for patients undergoing noncardiac than cardiac procedures, with significantly greater variation in average perioperative glucose (Fig. 2) as previously shown in Table 1.

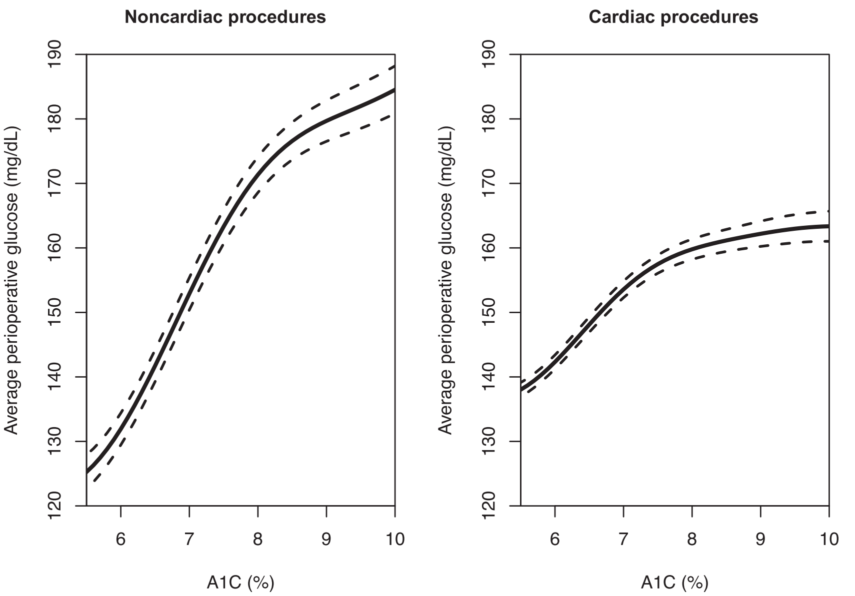

Figure 2—Average perioperative glucose level versus preoperative A1C percentage. Visual summary of the association between preoperative A1C and the average of glucose from the day of surgery through postoperative day 2 from the generalized additive model fit on the 6,684 noncardiac (left) and 6,393 cardiac surgeries (right). The solid line is the mean prediction and the dashed lines the 95% CIs.

Supplementary Fig. 2 illustrates the same analysis but only includes cases with a diabetes diagnosis as documented through ICD codes in the data. The main difference with Fig. 2 is that the perioperative glucose is higher at low levels of preoperative A1C.

30-Day Postoperative Mortality

Figure 3 shows the associations between postoperative mortality and A1C, average perioperative glucose, age, and BMI. Supplementary Tables 1 and 2 provide the results in tabular format, also when not controlling for glucose. For noncardiac surgeries, increased mortality was associated with female sex (odds ratio 1.8 [95% CI 1.2–2.7]; $P = 0.004$), very low BMI ($P = 0.001$), lower A1C ($P = 0.01$), increased age ($P < 0.001$), and increased average perioperative glucose ($P = 0.04$) after controlling for other predictors. In cardiac surgeries, increased mortality was associated with increased age ($P < 0.001$), BMI ($P = 0.001$), and both low and high average glucose ($P < 0.001$). Of note, A1C was not a significant ($P = 0.88$) predictor of postoperative mortality in cardiac surgeries.

The results demonstrate a clear effect of glycemic control on postoperative mortality. Furthermore, they illustrate a notably different relationship in noncardiac versus cardiac procedures. The association between average perioperative glucose and 30-day mortality was linear for noncardiac procedures, whereas it was U-shaped for cardiac procedures and was strongly associated with 30-day mortality outside of 120–160 mg/dL. The mortality levels corresponding to a glucose of 100, 140, and 200 mg/dL were 1.0% (95% CI 0.7–1.6%), 1.3% (95% CI 0.9–1.8%), and 1.6% (95% CI 1.1–2.3%) for noncardiac and 4.5% (95% CI 2.3–8.7%), 1.5% (95% CI 1.0–2.1%), and 6.9% (95% CI 3.3–14.1%) for cardiac cases, respectively. Controlling for blood glucose levels, A1C did not predict increased 30-day mortality despite the strong relationship between A1C and glucose in Fig. 2. In fact, A1C exhibited a negative association with 30-day mortality in noncardiac procedures after adjustment for glucose and other factors.

Supplementary Fig. 3 shows that there was no evidence of a difference in the cases studied in this study versus those with a diabetes diagnoses as documented via ICD codes in the data.

The Effect of Preoperative A1C, Different Time Windows, and Postoperative Mortality

A1C was negatively associated with 30-day mortality in noncardiac procedures after controlling for glucose, age, BMI, and sex. This changed for longer time windows for mortality. Supplementary Fig. 4 contains similar A1C plots as Fig. 3 with probability of 3-year and time-unlimited mortality on the *y*-axis. As the time window increased, the association of A1C with mortality became more positive. This was despite using the conservative approach of treating right-censored individuals as survivors: mortality records continued up to 2015, whereas the last procedure occurred <3 years prior, in 2013. When not controlling for perioperative blood glucose, the trend of mortality versus A1C, as shown in Fig. 3 and Supplementary Fig. 2, remained largely the same for noncardiac surgeries. However, the association became more positive for cardiac procedures than when controlling for perioperative glucose.

CONCLUSIONS

A retrospective analysis of electronic medical records from the Duke University Health System demonstrates that preoperative A1C predicts average perioperative blood glucose (3 postoperative day average) and that the average perioperative glucose predicts 30-day mortality. However, after controlling for age, BMI, sex, and perioperative glucose, elevated preoperative A1C was not positively associated with 30-day mortality. These statements held across both noncardiac and cardiac procedures, although the nature of the relationships differed between noncardiac and cardiac procedures.

The expected positive association between A1C and average perioperative glucose was present but not linear. This deviates from the common linear translation (8) of A1C to average glucose and was different between cardiac and noncardiac surgical populations. These differences are likely due to aggressive treatment of hyperglycemia with intravenous insulin in the perioperative setting in patients undergoing cardiac surgery.

Our results clearly demonstrate an association between average perioperative blood glucose levels and 30-day mortality. In noncardiac surgeries, higher average blood glucose was associated with higher 30-day mortality. The relationship between average glucose and mortality was notably different in patients undergoing cardiac surgery. We found a striking U-shaped curve in which average perioperative blood glucose of <120 or >160 mg/dL was associated with a marked increase in 30-day mortality in patients undergoing cardiac surgery. The distinct glucose-mortality relationships between cardiac and noncardiac surgery suggest

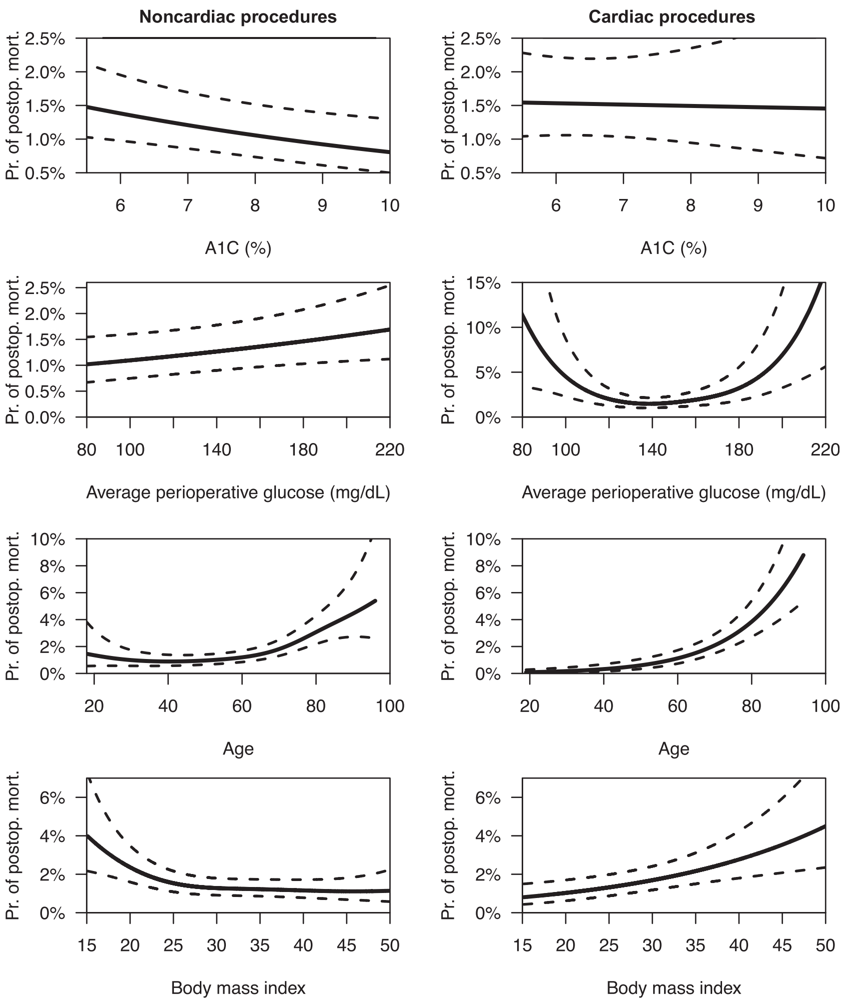

Figure 3—Probability of postoperative mortality (Pr. of postop. mort.) versus A1C, glucose, age, and BMI. Visual summary of the associations between 30-day postoperative mortality and preoperative A1C, average of glucose measurements from day of surgery up to postoperative day 2, age, and BMI from the generalized additive logistic model fit on the 6,684 noncardiac (left) and 6,393 cardiac surgeries (right). The solid line is the estimated probability and the dashed lines the 95% CIs.

a complex, variable interaction between glucose metabolism and postoperative recovery.

The U-shaped curve in cardiac surgery confirms the previously established harm of both perioperative hypoglycemia and hyperglycemia. Current American Diabetes Association guidelines recommend a target glucose range of 80–180 mg/dL in the perioperative period, with consideration of a lower target (<140 mg/dL) in select patients such as those who underwent cardiac surgery if the goal can be obtained without hypoglycemia (31). The Canadian Diabetes Association mentions a target range of 90–180 mg/dL (32). Further, the Society of Thoracic Surgeons recommends maintaining blood glucose in patients undergoing cardiac surgery <180 mg/dL irrespective of a diagnosis of diabetes (33). These targets are slightly more liberal than our results would suggest for patients who have had cardiac surgery, particularly regarding values in the lower end of the target range.

Our finding of increased mortality with tightly controlled blood glucoses is similar to the findings demonstrated in the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) (34) trial that showed higher mortality in critically ill patients randomized to intense blood glucose control (81–108 mg/dL) compared with a more moderate target of <180 mg/dL. Hypoglycemia itself increases risk of mortality. The mechanism for increased mortality in patients with tightly controlled blood glucoses may be related to adverse cardiovascular effects from lowering glucose with insulin (34). Experimental studies have shown that insulin and hypoglycemia can cause vasodilatation, hypotension, and exhaustion of the sympathetic system response. Further, the risk of frank hypoglycemia is higher when glucoses are tightly controlled, and recent hypoglycemia reduces the physiological response to subsequent hypoglycemia (35). Further research is needed to understand this complex interplay of insulin, hypoglycemia, and cardiovascular effects.

There have been conflicting results when looking at the association between increased A1C and mortality, with some investigators demonstrating increased mortality (6,12–14), whereas others (10,11,36) have not. Unfortunately, these studies examined small groups of patients undergoing a specific type of surgery or considered one rare outcome, whereas our data included many patients undergoing a broad variety of procedures. In our study, an elevated preoperative A1C was not predictive of increased 30-day mortality in either patients who had noncardiac surgery or patients who had cardiac surgery after controlling for blood glucose, despite the strong positive association between A1C and average perioperative glucose. These findings suggest that perioperative glycemic control may neutralize the effect of high A1C on postoperative mortality. It is possible that a high A1C, signifying uncontrolled or more difficult to control disease, might prompt more vigilance and aggressive treatment from perioperative clinicians.

Interestingly, a negative association was found between preoperative A1C and 30-day mortality in noncardiac surgeries. This is probably driven by very low A1C corresponding with high postoperative mortality, as found previously (18,19). Further, low BMI corresponded with higher mortality in noncardiac procedures similar to the trend noted in a multivariate analysis in cancer survival (37). Baseline nutritional status or decreased physiological reserve for another reason may be contributors. Additionally, the negative association between A1C and mortality in noncardiac surgeries may be partially confounded by acute physician intervention—for instance, if those with higher A1C are treated more aggressively in the perioperative and close postoperative periods. To determine the long-term association of A1C and mortality in light of no or even negative short-term effect, we extended the time frame for mortality. Over subsequent years, an elevated preoperative A1C was associated with long-term mortality in our patients, which is consistent with existing literature (18), providing further validation of our findings.

There are limitations to our study. These are retrospective data extracted from electronic medical records and, as such, subject to known weaknesses and biases. Less than one-tenth of the patients who had noncardiac procedures had preoperative A1C. Table 1 shows that those who did are older, more overweight, have higher mortality, and are more often male. Existence of an A1C measurement may reflect the diagnosis of diabetes or concern for the health status of a patient. We are, however, most interested in this subset of the population as we believe that this will better inform practice within this group. This relates to the limitation that we were unable to definitely say which of these patients carried a preoperative diagnosis of diabetes or were receiving glycemic therapy, both known to influence the relation between hyperglycemia and postoperative outcomes (1,38). Also, as other important adverse outcomes were not reliably captured, we limited ourselves to mortality.

Similarly, observational studies like this cannot prove causation. We are unable to state that improved perioperative glucose control is directly responsible for decreased mortality, only that they are associated. Interestingly, a patient who is deferred for elective surgery due to an elevated A1C may well be accepted after achieving a more favorable A1C target. Whether this actually improves their risk profile or the odds of achieving successful perioperative glucose control is unknown. Although previous randomized studies (39) have established the effect of specific blood glucose management strategies on glucose and A1C, they did not focus on mortality as an outcome. Such work is necessary to determine the effectiveness of using A1C as a screening tool in the elective surgery population.

We also recognize that the measurement of an A1C level has inherent limitations. These include possible racial and ethnic differences, particular hemoglobinopathies, and other conditions that shorten the life span of the erythrocyte or otherwise falsely lower or elevate A1C (40). Also, there are many factors that impact perioperative glucose control that were not examined in this analysis including but not limited to the use of cardiopulmonary bypass; choice of pharmacologic agent, dose, and strategy to treat hyperglycemia; intensity of nursing care; and patient comorbidities.

In conclusion, we sought to clarify the relationships among preoperative A1C, perioperative glucose control, and postoperative mortality as they inform the current practice of using preoperative A1C as a screen in offering elective surgery. Preoperative A1C was indeed a good predictor of a patient's average perioperative glucose level. Further, perioperative glucose was associated with 30-day mortality, linearly in noncardiac and strongly U-shaped in cardiac procedures. However, taking age, BMI, and perioperative glucose into account, A1C did not predict 30-day mortality other than at extremely low levels and, even then, only in patients who had noncardiac surgery. Thus, our results suggest that perioperative glucose control may be more important than preoperative A1C in predicting 30-day postoperative mortality.

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Author Contributions. W.v.d.B. and G.-O.F. conducted the analysis of data and produced an initial draft of the manuscript. R.A.S. conceived the study. R.A.S., M.W.M., T.L.S., and D.B.D. contributed to the interpretation of the results and editorial review and revision of the manuscript. W.v.d.B. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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