Factors Associated With Cardiovascular Events in Patients With Type 2 Diabetes and Acute Myocardial Infarction

Krzysztof Strojek, Itamar Raz, György Jermendy, Anselm K. Gitt, Rong Liu, Qianyi Zhang, Scott J. Jacober, and Zvonko Milicevic

Internal Diseases (K.S.), Diabetology and Cardiometabolic Diseases, Silesian Centre of Heart Diseases, Silesian Medical University, 41-800 Zabrze, Poland; Diabetes Unit (I.R.), Internal Medicine Department, Hadassah Hebrew University Medical Center, Jerusalem 91120, Israel; Medical Department (G.J.), Bajcsy-Zsilinszky Teaching Hospital, Budapest, 1106 Hungary; Cardiology (A.K.G.), Herzzentrum Ludwigshafen, Medizinische Klinik B, 67063 Ludwigshafen, Germany; Eli Lilly and Company (R.L., Q.Z., S.J.J.), Indianapolis, Indiana 46285; and Lilly Regional GmbH (Z.M.), Eli Lilly and Company, 1030 Vienna, Austria

Context: Decreasing risk of cardiovascular (CV) disease remains a challenge to survival in type 2 diabetes.

Objective: The objective was to assess the association between demographic, glycemic, and other clinical factors and CV risk in the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus trial.

Design, Settings, Participants, and Intervention: We used discrete-time survival tree analysis to examine data collected for up to 4.6 years in 1115 patients with type 2 diabetes mellitus experiencing acute myocardial infarction (MI) less than or equal to 18 days before enrollment.

Main Outcome Measures: The primary objective was to identify demographic, glycemic, and CV risk factors best separating survival curves over time for a composite end point: CV death, nonfatal MI, nonfatal stroke, hospitalization for acute coronary syndromes, or coronary revascularization planned after randomization.

Results: Average change across visits in mean 2-hour blood glucose level after meals was associated with the greatest difference in event-free survival probability for the primary end point: mean time to 75% event-free survival for an average change across visits less than or equal to −0.14 mmol/L, 73.48 weeks; for visits with average change more −0.14 mmol/L, 29.10 weeks. An average change across visits in the hemoglobin A_{1c} level less than or equal to −0.92% (−10.06 mmol/mol) and the absence of a history of stroke or acute MI increased CV event-free survival time further. Fasting blood glucose and randomized insulin treatment strategy were weak predicting factors of event-free survival.

Conclusions: Postprandial glycemia should be considered a potential target in trials to reduce CV morbidity and mortality in type 2 diabetes mellitus. **(*J Clin Endocrinol Metab* 101: 243–253, 2016)**

In epidemiological studies, postprandial and postglucose challenge hyperglycemia has been linked to the risk of cardiovascular (CV) disease (1–3), the leading cause of morbidity and mortality in patients with diabetes (3–5). Whether the association between postprandial hyperglycemia and CV disease is independent of other measures of

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Abbreviations: ACS, acute coronary syndrome; BG, blood glucose; CABG, coronary artery bypass graft; CV, cardiovascular; DTST, discrete-time survival tree; HEART2D, Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with type 2 Diabetes Mellitus; HbA_{1c}, hemoglobin A_{1c}; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

glycemic control, such as the hemoglobin A_{1c} (HbA_{1c}) and fasting/premeal blood glucose (BG), or other CV risk factors, remains unclear (6, 7). Data from prospective interventional trials targeting specifically postprandial vs fasting/premeal hyperglycemia to reduce the risk of acute myocardial infarction (MI), stroke, CV mortality, and other CV events are of key importance in resolving this question.

The Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with type 2 Diabetes Mellitus (HEART2D) trial was designed to assess the effect of postprandial hyperglycemia on the risk of occurrence of CV events in 1115 patients with type 2 diabetes mellitus and recent acute MI. The patients were randomized to one of 2 insulin treatment strategies: a strategy targeting postprandial hyperglycemia or a strategy targeting fasting/premeal hyperglycemia. It was hypothesized that these 2 treatment approaches might result in a similar HbA_{1c} level with differences in daily fasting/premeal and postprandial glycemia between the groups that would allow assessment of the effect of postprandial glycemia on CV outcomes. The study was stopped early for futility because of a lower than expected event rate and low probability of reaching the expected difference in event rate between the 2 arms. Another key issue in HEART2D was a separation in postprandial glycemia levels between the 2 groups that was much smaller (0.8 mmol/L) than required by the statistical power calculations (2.5 mmol/L) to evaluate the primary objective of the trial to assess the effect of postprandial glycemia on risk of CV events (8).

In the absence of definitive data on the CV risk attributable specifically to postprandial glycemia, epidemiological assessments are important for developing hypotheses to be further evaluated in future interventional trials. One common problem in reported epidemiological studies is limited availability of prospectively collected patient-level data for self-monitored BG and other variables of interest. The HEART2D database provides an opportunity to overcome this problem, because the HEART2D investigators systematically collected data on CV outcomes, standard CV risk factors, and variables of glycemic control for up to 4.6 years (9, 10).

The objective of the analyses presented here was to identify the most relevant factors associated with individual and composite CV outcome measures in the overall HEART2D population, irrespective of the randomization assignment. Considering that the Cox model is associated with significant limitations in handling correlated factors, alternative statistical methods, the classification and regression tree (11) and the discrete-time survival tree (DTST) (12) approaches, were considered. Because the DTST method by Bou-Hamad et al (12), unlike classification and regression tree, can accommodate both time-independent (eg, demographics, treatment assignment) and time-dependent (eg, HbA_{1c} measured at different time points) factors and irregular time intervals between assessments, it was considered better suited for the analyses planned in this study. This method allows assessments of individual factors across the entire postrandomization period, as well as the last values collected before the occurrence of an event of interest.

Subjects and Methods

The HEART2D study design and the population that participated in the trial are described in detail elsewhere (13, 14). In brief, patients were eligible if they were at least 30 years old, had type 2 diabetes mellitus, and experienced an acute MI within 3 weeks before study entry. They were enrolled less than or equal to 18 days after hospital admission for acute MI and were randomized to one of 2 groups less than or equal to 21 days after admission: 1) the prandial insulin strategy group or 2) the fasting/premeal insulin strategy group. Patients in the prandial group were treated with mealtime insulin lispro (Humalog, Eli Lilly and Company). Patients in the fasting/premeal group were treated with 2 daily doses of neutral protamine Hagedorn (isophane) insulin (Humulin, Eli Lilly and Company) or a single daily dose of insulin glargine (Lantus; Sanofi). Patients were to be treated for a minimum of 18 months.

The primary outcome was the same as that of the HEART2D trial—a composite of CV death, nonfatal MI, nonfatal stroke, hospitalization for acute coronary syndromes (ACSs), or a coronary revascularization planned after randomization. The secondary outcome measures were 1) CV death, 2) nonfatal MI, 3) nonfatal stroke, and 4) a composite of these 3 outcomes. Censoring was defined separately and independently for each given outcome; that is, if a patient was discontinued from the study because of the occurrence of one outcome (other than CV death), the patient was still counted as censored for other outcomes.

In all, 24 time-independent and 50 time-dependent factors (see Tables 1 and 2 and Supplemental Figure 1) were selected as potential variables of interest for assessment. For brevity, we refer to all as factors. They included both continuous and categorical variables, and data were, by protocol, collected at a minimum at baseline and at up to 12 subsequent visits. Intervals between visits ranged from 10 days to 26 weeks. Patients were asked to perform three 7-point BG profiles in the 4 weeks before each visit, with a maximum of one 7-point profile per week. These profiles consisted of BG measurements before and 2 hours after the morning, midday, and evening meals, as well as a fasting measurement the next day.

Statistical analysis

We applied the DTST method (12) to build a tree model for each outcome of interest. Each tree started from the root node containing all patient visits and then branched out to the tree nodes defined by the best splitting factors and their corresponding cutoff values. See the Statistical analysis appendix in

Table 1. Time-Independent Factors

Category	Factors
Demographics	
Demographics	Gender, origin, duration of DM
Diabetes mellitus	
Antihyperglycemia treatment	Current diabetes treatment, predominant treatment in last year, predominant treatment in last 5 y, and insulin infusion for index event
Treatment strategy	Insulin strategy targeting postprandial or fasting/premeal glycemia
CV disease	
Acute MI	Type, treatment
CV disease in medical history	Previous MI or previous stroke
CV medications	Angiotensin-converting enzyme medication, angiotensin receptor blockers, β-blockers, statins, aspirin, and clopidogrel
Lipids	Total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides
Cardiac function	Left ventricular ejection fraction, QT interval
Coronary imaging	Planned coronary angiography

DM, diabetes mellitus. Checks indicate measures included. Antihyperglycemia treatment classifications included diet, sulfonylurea, metformin, and insulin.

the Supplemental Material and Methods for more details on DTST.

To show that we comprehensively considered the entire set of factors for each split, we reported the top 5 candidate factors of each tree node. The following information characterizes the effect of splitting: splitting rule by the corresponding cutoff value; number of patient visits meeting the rule; time to 75% event-free survival (wk); event-free survival probability at weeks 26, 52, and 78; and improvement in the value of the splitting criterion (log-likelihood function) after splitting.

Because HbA_{1c} data were not collected at visit 3 (wk 5 after randomization), and there were 57 (16.1%) combined CV events during this early period before the first postrandomization HbA_{1c} measurement, the estimate of the association between HbA_{1c} and outcomes might have been impacted by the missing data. To evaluate, we conducted a sensitivity analysis by imput-

Table 2. Time-Dependent Factors

	At Visit		Average Across Visits	
Factor	Actual Measurement	Change From Baseline	Actual Measurement	Change From Baseline
Demographics				
Weight	√			
Body mass index	√			
Smoking	√			
Exercise	√			
Urinary albumin to creatinine ratio (mg/g)	√			
Diabetes-related Factors				
Average of 3 daily 2-hour BG levels after breakfast, lunch, and dinner	√	√	√	√
Average of all 3 daily 2-hour BG excursion levels after breakfast, lunch, and dinner	√	√	√	√
Two-hour BG levels after breakfast	√	√	√	√
Two-hour BG excursion levels after breakfast	√	√	√	√
Fasting BG levels	√	√	√	√
Average of 3 daily BG measures before breakfast, lunch, and dinner	√	√	√	√
HbA_{1c} level	√	√	√	√
Total hypoglycemia rate per 30 days	√		√	
Total hypoglycemia incidence	√		√	
Severe hypoglycemia incidence	√		√	
Total nocturnal hypoglycemia incidence	√		√	
Total nocturnal hypoglycemia rate	√		√	
Insulin daily dose (U/kg body weight)	√			
Vital parameters				
Heart rate	√		√	
Systolic blood pressure	√		√	
Diastolic blood pressure	√		√	

Checks indicate measures included.

ing HbA_{1c} values at the week 5 visit using linear interpolation (15) based on the HbA_{1c} levels from adjacent visits (baseline and wk 13). The sensitivity analysis was then reapplied using the DTST on the imputed data.

Analyses were performed using R, version 2.15.1 (R Core Team, R Foundation for Statistical Computing).

Results

Patients

The HEART2D trial included 1115 randomized patients (706 men, 409 women). One patient from the intent-to-treat population discontinued immediately after randomization and did not contribute data to the analysis. The mean duration of follow-up after randomization was 2.7 years (range, 1 d to 4.6 y). At baseline, mean age was 61.0 (range, 32.1–84.1) years; mean duration of diabetes, 9.2 years; mean body mass index, 29.1; and mean HbA_{1c}, 8.4% (68.3 mmol/mol). Patient baseline characteristics are described in Table 3, and additional clinical and demographic characteristics are reported elsewhere (8).

Primary outcome: Factors that predict events from composite CV end point

Table 4 presents the 5 factors with the greatest separation between event-free survival curves for the primary outcome, time to the first event from the composite end point of CV death, nonfatal MI, nonfatal stroke, hospitalization for ACSs, and planned coronary revascularization, at weeks 26, 52, and 78 within the first split. An average change across visits in mean 2-hour BG levels after meals (breakfast, lunch, and dinner) less than or equal to −0.14 mmol/L identified patient visits less likely to be associated with a CV event. Time to 75% event-free survival was 29.10 weeks for visits with values more than −0.14 mmol/L and 73.48 weeks for those with values less than or equal to −0.14 mmol/L. The other important candidate factors for the first split were change from baseline to visit in HbA_{1c} level, average change across visits in HbA_{1c} level, change from baseline to visit in 2-hour after-breakfast BG, and average change across visits in 2-hour after-breakfast BG.

At the second split for the primary outcome (or the second layer of the tree), the average change across visits in HbA_{1c} value of −0.92% (−10.06 mmol/mol) had greater effect than other factors (time to 75% survival: >−0.92% [−10.06 mmol/mol], 96.28 wk; ≤−0.92% [−10.06 mmol/mol], 156.00 wk) (Table 4). The other candidate factors for the second split were as following: change from baseline to visit in HbA_{1c} level, HbA_{1c} level at visit, exercise status, and the total hypoglycemia event rate per 30 days (at visit).

Table 3. Baseline Demographic and Selected Clinical Characteristics of the HEART2D Trial Population

Variable	n	%
n	1115	100.0
Sex		
Female	409	36.7
Male	706	63.3
Age (y)		
Mean (range)	61.0 (32.1–84.1)	
Age ≥65	422	37.9
Race/regional origin group		
White	967	86.7
Western Asian	119	10.7
African descent	7	0.6
Other	22	2.0
Education (n = 1101)		
Elementary school	377	33.8
High school	440	39.5
University	173	15.5
Vocational school	111	10.0
Weight (kg) (n = 1113)	81.5 ± 15.5	
BMI (n = 1113)		
Mean (range)	29.1 (17.4–57.5)	
<25	217	19.5
≥25	896	80.5
Duration of diabetes (y)[a]	9.2 ± 7.2	
HbA_{1C}		
%	8.4 ± 1.5	
mmol/mol	68.3 ± 16.4	
Current tobacco use	174	15.6
Systolic blood pressure (mm Hg)	127.3 ± 17.2	
Diastolic blood pressure (mm Hg)	76.7 ± 9.3	
Previous MI	200	17.9
Thrombolysis (recent acute MI)	195	17.5
Intravenous insulin infusion (recent acute MI)	324	29.1
CABG (recent acute MI)	30	2.7
PTCA (recent acute MI)	481	43.1
Urinary albumin to creatinine ratio (mg/g)	138.4 ± 526.7	
QTc interval (ms)	434.6 ± 33.3	
Left ventricular ejection fraction (%)	50.8 ± 10.1	

BMI, body mass index; HbA_{1c}, glycated hemoglobin; PTCA, PTCA calculated from primary PTCA and PTCA stents. Data are reported as mean ± SD, mean and range or n (%). One patient who was randomized but never again had a study visit after randomization was not included in the analysis by the discrete-time tree survival method. Previous MI refers to any MI before study-qualifying event.

[a] Inclusion criteria required the study population to have type 2 diabetes, according to World Health Organization criteria, for at least 3 months after acute MI. At baseline, the most common therapies were administration of sulfonylureas (25.9%), insulin (conventional regimens) (22.3%), and metformin plus sulfonylureas (15.4%).

At the third split for the primary outcome (or the third layer of the tree), the absence of a history of acute MI or stroke was the factor associated with the greatest additional risk reduction (Table 4). At this final split, the time to 75% event-free survival within the node was more than 3 times longer for those without a history of an acute MI or stroke than for those with such a history (history of event, 65.08 wk; no history of event, >208.00 wk). The

Table 4. Time to 75% Event-Free Survival by Splitting Factors and Their Cutoff Values

Top Factors for Splitting	Number of Visits[a]	Splitting Criterion (Log-Likelihood Improvement)	Event-Free Survival Probability (% of Patient Visits)			Time to 75% Event-Free Survival (wk)
			At 26 Weeks	At 52 Weeks	At 78 Weeks	
Primary outcome (composite CV events): First split[b]						
Average change across visits in mean 2-hour BG level after breakfast, lunch, and dinner		62.65				
>−0.14 mmol/L	2515		75.47	72.37	68.31	29.10
≤−0.14 mmol/L	4977		84.53	77.29	74.52	73.48
Change from baseline to visit in HbA_{1c} level		61.68				
>−0.2% (−2.19 mmol/mol)	2772		83.84	78.15	75.04	78.56
≤−0.2% (−2.19 mmol/mol)	3332		88.69	80.87	77.64	116.99
Average change across visits in HbA_{1c} level		61.35				
>−0.15% (−1.64 mmol/mol)	2613		83.21	77.53	74.48	73.54
≤−0.15% (−1.64 mmol/mol)	3491		88.96	81.19	77.93	119.45
Change from baseline to visit in 2-hour after-breakfast BG level		61.31				
>−0.18% mmol/L	2392		79.97	74.91	69.69	51.12
≤−0.18% mmol/L	5027		82.96	76.67	74.09	68.81
Average change across visits in 2-hour after-breakfast BG level		61.28				
>−3.55 mmol/L	2336		78.23	71.92	67.08	41.69
≤−3.55 mmol/L	5083		83.37	77.29	74.60	74.13
Primary outcome (composite CV events): Second split[b]						
Average change across visits in HbA_{1c} level		22.92				
>−0.92% (−10.06 mmol/mol)	1918		89.06	80.43	76.21	96.28
≤−0.92% (−10.06 mmol/mol)	1970		91.35	83.95	81.97	156.00
Change from baseline to visit in HbA_{1c} level		21.23				
>−0.9% (−9.84 mmol/mol)	1896		88.94	80.11	76.67	100.45
≤−0.9% (−9.84 mmol/mol)	1992		91.33	84.11	81.42	156.00
HbA_{1c} level		19.09				
>6.8% (50.81 mmol/mol)	3363		85.21	78.76	76.72	106.37
≤6.8% (50.81 mmol/mol)	1559		85.91	77.01	72.78	64.37
Exercise		18.77				
No	4550		84.50	77.35	74.58	74.03
Yes	427		95.24	89.47	89.47[c]	208.00+[d]
Total hypoglycemia event rate per 30 days		16.56				
>0.33	1234		79.38	70.20	64.51	37.55
≤0.33	3743		86.60	80.14	78.23	134.35
Primary outcome (composite CV events): Third split[b]						
History of acute MI or stroke		17.79				
No	1234		92.66	88.34	87.80	208.00+[d]
Yes	736		89.41	77.49	72.54	65.08
Daily insulin dose at visit		16.14				
>0.70 U/kg	400		94.24	82.13	76.56	102.41
≤0.70 U/kg	1570		90.74	84.66	83.79	156.00
Average change across visits in HbA_{1c} level		14.86				
>−1.31% (−14.32 mmol/mol)	454		93.53	79.15	75.38	79.40
≤−1.31% (−14.32 mmol/mol)	1516		90.56	85.44	84.10	191.24
HbA_{1c} level		14.60				
>6.6% (48.62 mmol/mol)	1398		92.28	85.37	83.97	163.44
≤6.6% (48.62 mmol/mol)	572		89.49	80.86	77.45	92.52

(*Continued*)

Table 4. Continued

Top Factors for Splitting	Number of Visits[a]	Splitting Criterion (Log-Likelihood Improvement)	Event-Free Survival Probability (% of Patient Visits)			Time to 75% Event-Free Survival (wk)
			At 26 Weeks	At 52 Weeks	At 78 Weeks	
Change from baseline to visit in fasting BG level		13.75				
>−1.23 mmol/L	773		96.18	91.05	88.75	172.87
≤−1.23 mmol/L	1192		88.35	79.55	76.83	106.69
Secondary outcome (CV death): First and only split						
Treatment for acute MI (index event)		23.06				
Any pharmacological treatment (antiaggregation, anticoagulation, or IV catecholamines) without reperfusion	3589		93.69	90.33	87.90	208.00+[d]
PTCA, CABG, thrombolysis, or no treatment	5595		98.87	97.82	97.09	208.00+[d]
Secondary outcome (acute MI): First and only split						
Change from baseline to visit in mean BG level before breakfast, lunch, and dinner		23.70				
>−0.66 mmol/L	4166		93.18	89.86	89.24	208.00+[d]
≤−0.66 mmol/L	4448		94.85	92.39	91.29	208.00+[d]
Secondary outcome (CV death and/or acute MI and/or stroke): First split						
Average change across visits in HbA_{1c} level		34.39				
>−0.49% (−5.36 mmol/mol)	3498		91.14	85.80	83.73	175.37
≤−0.49% (−5.36 mmol/mol)	3496		95.76	91.98	89.64	208.00+[d]
Secondary outcome (CV death and/or acute MI and/or stroke): Second split						
Change from baseline to visit in HbA_{1c} level		19.37				
>0% (0 mmol/mol)	1524		95.98	91.80	89.86	208.00+[d]
≤0% (0 mmol/mol)	1974		88.28	81.14	78.73	160.18

For the primary outcome, the top 5 candidate factors are presented for each split; for the secondary outcomes, the top splitting factor is presented for each split. No split was identified for the secondary outcome of stroke.

[a] The path a patient's data take on a DTST depends on the status of the factors at a given visit. If a split is based on a time-dependent factor, some patients may have visits that fall into both nodes of the split. Provided here is the number of patient visits assigned to each node (ie, the number of visits with data for the corresponding candidates in the corresponding tree node).

[b] The composite of CV events includes CV death, nonfatal MI, nonfatal stroke, hospitalization for acute coronary symptoms, or a coronary revascularization planned after randomization.

[c] Measure reported is for visit 7 (52 wk).

[d] The survival probability was >75% at the last visit; therefore, the time to 75% survival exceeded the duration of the trial.

remaining 4 of the 5 candidate factors for the third split were as following: daily insulin dose (U/kg body weight) at visit, average change across visits in HbA_{1c} level, HbA_{1c} level at visit, and change from baseline to visit in fasting BG level. Figure 1 shows the final selected tree obtained for the primary CV outcome.

A sensitivity analysis rebuilt the DTST on the data with imputed HbA_{1c} values after 5 weeks of treatment (visit 3). The tree in the sensitivity analysis had only 2 splits, one from the average change across visits in mean 2-hour BG values after meals (a value ≤−0.14 mmol/L was associated with greater survival probability) and the other from exercise status at visit (exercising was associated with greater survival probability) (see Supplemental Figure 2).

Secondary outcomes: Factors associated with CV death, acute MI, and stroke

The assessments of factors for secondary outcomes CV death, acute MI, stroke, and a combination of these 3 are presented in Table 4. No factor was strongly associated with improved event-free survival time for stroke. The most relevant splitting factor for CV death was the type of

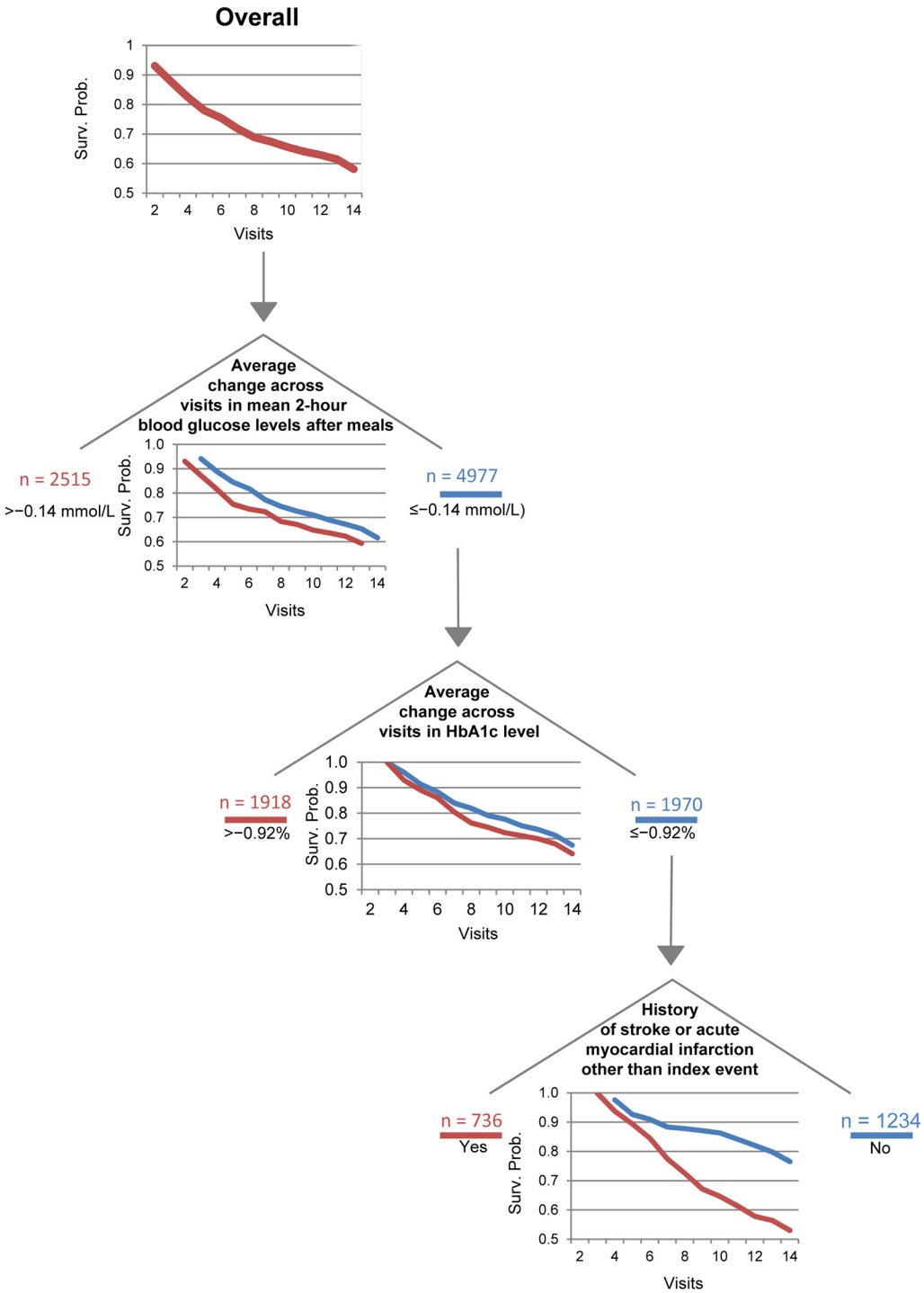

Figure 1. The DTST for composite CV outcome measure. An average change across visits from baseline in mean 2-hour BG level after breakfast, lunch, and dinner less than or equal to −0.14 mmol/L was identified as the factor associated with the greatest probability of extended survival (surv. prob., or survival probability). The DTST indicates that further changes in CV risk through each layer by the candidates associated with the greatest improvement (indicated in blue). An average change across visits in HbA_{1c} level less than or equal to −0.92% (−10.06 mmol/mol) and the absence of a history of acute MI or stroke before the qualifying MI were associated with improved survival. Numbers (Ns) are numbers of observations (visits).

treatment for the index, or qualifying, MI. Patients who received no specific treatment at all or received acute reperfusion treatment with or without antiplatelet or anticoagulation agents (such as primary percutaneous transluminal coronary angioplasty [PTCA], thrombolysis, or coronary artery bypass graft [CABG]) had greater survival probability than patients treated exclusively antiaggregation and/or anticoagulants and/or IV catecholamines (Figure 2). Other key candidates for this split were the following: average change across visits in mean BG level

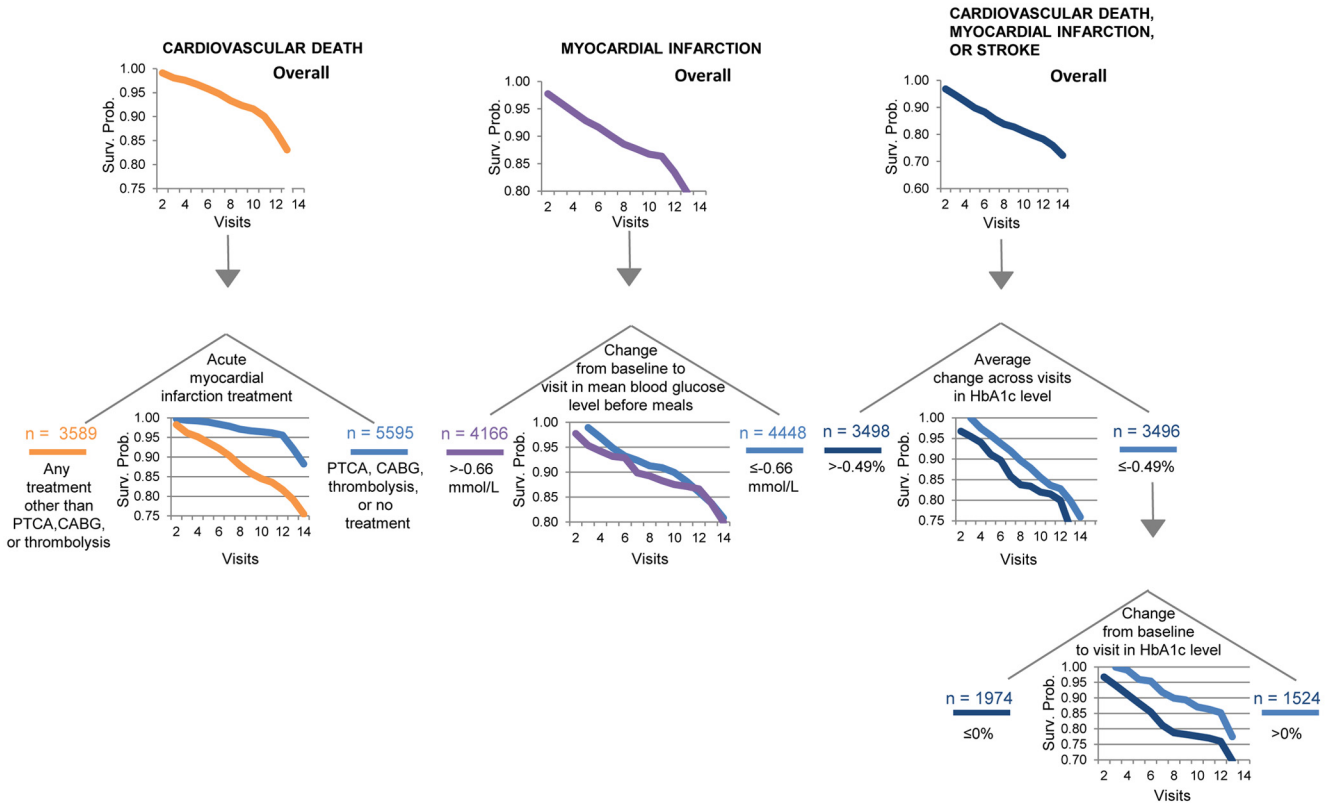

Figure 2. Secondary outcomes. Splitting variables were identified for 3 of 4 secondary outcomes; however, for stroke, no splitting variable associated with improved survival could be identified. Treatment options associated with extended survival for the secondary outcome of CV death included PTCA, CABG, thrombolysis, or absence of treatment. For risk of acute MI, a change in mean BG level before meals of less than or equal to −0.66 mmol/L was associated with greater event-free survival probability (surv. prob.), but time to 75% event-free survival extended beyond 208.00 weeks for both values. For the composite secondary outcome, an average change across visits in HbA_{1c} level less than or equal to −0.49% (−5.36 mmol/mol) was associated with extended event-free survival (time to 75% event-free survival: >−0.49% (−5.36 mmol/mol), 175.37 weeks; less than or equal to −0.49% (−5.36 mmol/mol), 208.00+ wk) for the first split and a change from baseline to visit in HbA_{1c} level more than 0% (0 mmol/mol) was associated with extended event-free survival in the second split (time to 75% event-free survival: >0% [0 mmol/mol], 208.00+ wk; ≤0% [0 mmol/mol], 160.18 wk).

before meals, duration of diabetes, mean BG before meals at visit, and change from baseline to visit in mean BG before meals. For all these factors, the association with CV death was weak, as indicated by low log-likelihood improvement (data not shown).

For the risk of acute MI, a change from baseline to visit in mean BG before meals less than or equal to −0.66 mmol/L was associated with higher overall event-free survival probability (Table 4 and Figure 2). The remaining candidates identified by the analysis as having predictive value were change from baseline to visit in 2-hour after breakfast BG, change from baseline to visit in fasting BG, change from baseline to visit in average 2-hour BG after meals, and average change across visits in 2-hour after breakfast BG. Similar to that for CV death, the association between these factors and acute MI was weak, as suggested by low log-likelihood improvement.

For the combined outcome of CV death, nonfatal MI, or nonfatal stroke, an average change across visits in HbA_{1c} level less than or equal to −0.49% (−5.36 mmol/mol) identified patient visits less likely to be associated with any event (Table 4 and Figure 2). The remaining 4 candidate factors with strongest association include the following: average change across visits in 2-hour after-breakfast BG, change from baseline to visit in the postbreakfast BG excursion, change from baseline to visit in the 2-hour after-breakfast BG, and change from baseline to visit in HbA_{1c}. The second splitting factor, a change from baseline to visit in HbA_{1c} more than 0% (0 mmol/mol), further improved event-free survival time in the first child node (or the subset of all patient visits) with an average change across visits in HbA_{1c} less than or equal to −0.49% (−5.36 mmol/mol). Other candidate factors associated with improved event-free survival time included the following: average change across visits in HbA_{1c} level, change from baseline to visit in postbreakfast BG excursion, change from baseline to visit in average 2-hour BG after meals, and the level of triglycerides at the visit.

Discussion

Here, we present the results of the assessment of associations between the occurrence of a new CV event and a large

number of individual potential candidate factors, including demographic variables, established CV risk factors, and diabetes-related variables in patients with type 2 diabetes and recent MI using the DTST method. The greatest difference in event-free survival for the primary outcome was observed between an average change across visits from baseline in mean 2-hour postprandial BG less than or equal to −0.14 mmol/L and visits with a value more than −0.14 mmol/L. An average change across visits in HbA_{1c} less than or equal to −0.92% (−10.06 mmol/mol) further improved survival time for the second split. In the third split, the absence of a history of acute MI or stroke before the index MI event further reduced the risk. None of the included factors was strongly or consistently associated with event-free survival for secondary outcomes of CV death, new MI, stroke, or the composite end point of these 3 outcomes.

The 2 time-dependent factors with the greatest separation in event-free survival time in the population included in this study were both diabetes-related: average change across visits in mean 2-hour postprandial BG and average change in HbA_{1c} across all visits. None of the factors related to fasting or premeal BG or randomized insulin treatment strategy was strongly associated with the measures of CV risk used in the analyses. In addition, the standard CV risk factors did not associate with the measure of CV risk strongly in this population. These results are consistent with some epidemiological reports showing increased CV risk in patients with greater postprandial BG increases independent from HbA_{1c} or fasting BG (16, 17). Although recently reported large interventional trials did not show reduction in the risk of new CV events in patients with greater reduction in overall glycemia as measured by HbA_{1c}, these studies did not specifically focus on the components of daily BG (fasting/premeal vs postprandial) (18–20). The HEART2D trial is the only interventional study to date that aimed to assess CV risk with respect to differences in the postprandial period, but the study was stopped early without providing a definitive answer to this question. Consistent with other large interventional trials in patients with type 2 diabetes, results of our post hoc assessment of the HEART2D database suggest a weak association between HbA_{1c} and CV outcomes and a notable role of postprandial abnormalities in such outcomes.

Although our primary interest was to generate more data to guide future interventional research in CV disease in type 2 diabetes, at least 2 aspects of the analyses presented here may be of relevance in the clinical setting. Current guidelines for management of type 2 diabetes recognize the importance of achieving control over postprandial hyperglycemia for the overall success of long-term disease therapy (21). The results presented here are, in general, consistent with this position, despite their post hoc nature. It is also important to note that both factors (2-hour postprandial glucose and HbA_{1c}) with strongest association with CV outcomes represent the effects on the variable of interest over the entire observational period (across all visits) rather than at a single time point (for example, just before the occurrence of a CV event). This may indicate that chronic (or cumulative) effects of these glycemic variables are of greater importance for the risk of macrovascular complications of diabetes than the acute (or short-term) abnormalities before the events of interest.

The analysis presented here differs from others already reported in the medical literature in several important aspects. The HEART2D database consists of prospectively collected data with repeated measurements of variables potentially important in determining the risk of new CV events. In available epidemiological reports these parameters have been assessed mostly at baseline without any further insight during the observational period (22–25). The DTST method was chosen for this analysis because it accommodates not only data collected at the beginning and end of the study but also all available repeated measurements for a number of potential predicting factors during the entire period of interest. In this application, this method has a number of advantages over the traditional multivariate survival method of the Cox proportional hazards regression model. It makes no assumptions about the underlying distribution of data, the relationship between the factors and hazard function, and the independence of factors. The DTST method also overcomes several other limitations of the Cox model, especially in handling highly correlated factors (eg, self-monitored BG levels and hypoglycemia incidence, average change across visits in HbA_{1c} level, and change from baseline in HbA_{1c}) and incorporating time-varying information before an event. In the HEART2D study, intervals between visits were longer near the end of the study, and this statistical method also accommodates such variable data collection intervals.

We created a large list of factors, in part, because we intended to assess various aspects of each variable. For example, for HbA_{1c} and components of daily glycemia, several factors were created (eg, values measured at visits, averages across visits, changes from baseline, and values collected before an event, or censoring) in order to decrease uncertainty caused by the choices made before the study. This is of great importance for assessment of CV risk because various pathophysiological pathways potentially causally related to CV events may affect CV outcomes in these patients. For example, postprandial hyperglycemia may increase the risk by affecting the progression of the underlying chronic atherosclerotic process because of accumulating or chronic structural changes over time.

Another possibility relates to the acute, reversible effects on thrombogenesis, endothelial function, or function of the specialized cardiac conduction system (26–29). This pathophysiological complexity has significant implications for design of clinical studies aiming to assess the relationship between the risk factors and CV outcomes of interest. For example, duration of exposure to an intervention, if too short, may increase the probability of a negative outcome, when in fact, the intervention may be associated with benefit.

There are also several limitations of this study, including some that are related to its post hoc nature. There were no consistent observations across the analyses of primary and secondary outcomes. The 2-hour postprandial glucose across visits did not predict hard outcomes in the overall population, which may suggest its primary role in reducing coronary revascularizations and hospitalizations for ACS. Our study cannot provide answers to this question due to design-related limitations and may be addressed in future trials. In addition, certain aspects of overall glycemic exposure (or HbA_{1c}) and postprandial hyperglycemia may have a role in the risk of the clinically relevant outcomes of CV death, MI, and stroke. However, the associations were not strong for the composite end point that included these 3 outcomes, as indicated by low log-likelihood improvement values and small differences with respect to the event-free probabilities and time to event. A similar conclusion can be drawn about the assessment of individual outcomes of CV death, any MI, and any stroke. These results should be interpreted with caution because the number of events for each of these secondary outcomes was small.

Furthermore, the patient population that participated in HEART2D trial included those with very high risk for new CV events with potential limited importance of many of the factors analyzed. Therefore, the conclusions from this report can only be applied to patients with demographic and clinical characteristics of the HEART2D population. As discussed above (statistical analysis section), 16.1% of all postenrollment CV events occurred before the first postbaseline measurement of HbA_{1c}. This problem relates to the trial design and was addressed in a sensitivity analysis with imputed HbA_{1c} data, but the limitation remains. Finally, we used a 10-fold cross-validation, which is a standard approach; however, unless a test set is withheld, there are limitations in assessing the bias and predictive value.

In conclusion, the finding in this post hoc analysis that a reduction in the average change across visits in the mean 2-hour BG levels after meals had the strongest association (see splitting statistics in Table 4) with CV outcomes is supported by epidemiological evidence linking postprandial BG with increased risk of new CV events (8, 30). This may indicate that of the 2 components of HbA_{1c}, postprandial hyperglycemia may be a more important factor in the pathophysiology of CV disease than the fasting/interprandial glycemia. Although the results described here cannot be interpreted as indicating a causal relationship between any aspect of glycemia and CV outcomes, they do support potential relevance of postprandial hyperglycemia as a treatment target in future interventional trials. New interventional trials focusing on postprandial and fasting/premeal BG should be designed to overcome the design-related limitations of the HEART2D study, including a longer observational period and targeting patients in earlier stages of type 2 diabetes mellitus as well as those with significant postprandial hyperglycemia.

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Address all correspondence and requests for reprints to: Zvonko Milicevic, MD, PhD, Eli Lilly Regional Operations GmbH, Koelblgasse 8-10, A-1030 Vienna, Austria. E-mail: milicevic_zvonko@lilly.com.

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