

# Effects of Prandial Versus Fasting Glycemia on Cardiovascular Outcomes in Type 2 Diabetes: The HEART2D trial

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**OBJECTIVE** — Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) is a multinational, randomized, controlled trial designed to compare the effects of prandial versus fasting glycemic control on risk for cardiovascular outcomes in patients with type 2 diabetes after acute myocardial infarction (AMI).

**RESEARCH DESIGN AND METHODS** — Patients (type 2 diabetes, aged 30–75 years) were randomly assigned within 21 days after AMI to the 1) prandial strategy (PRANDIAL) (three premeal doses of insulin lispro targeting 2-h postprandial blood glucose <7.5 mmol/l) or the 2) basal strategy (BASAL) (NPH twice daily or insulin glargine once daily targeting fasting/premeal blood glucose <6.7 mmol/l).

**RESULTS** — A total of 1,115 patients were randomly assigned (PRANDIAL  $n = 557$ ; BASAL  $n = 558$ ), and the mean patient participation after randomization was 963 days (range 1–1,687 days). The trial was stopped for lack of efficacy. Risks of first combined adjudicated primary cardiovascular events in the PRANDIAL ( $n = 174$ , 31.2%) and BASAL ( $n = 181$ , 32.4%) groups were similar (hazard ratio 0.98 [95% CI 0.8–1.21]). Mean A1C did not differ between the PRANDIAL and BASAL groups ( $7.7 \pm 0.1$  vs.  $7.8 \pm 0.1\%$ ;  $P = 0.4$ ) during the study. The PRANDIAL group showed a lower daily mean postprandial blood glucose (7.8 vs. 8.6 mmol/l;  $P < 0.01$ ) and 2-h postprandial blood glucose excursion (0.1 vs. 1.3 mmol/l;  $P < 0.001$ ) versus the BASAL group. The BASAL group showed lower mean fasting blood glucose (7.0 vs. 8.1 mmol/l;  $P < 0.001$ ) and similar daily fasting/premeal blood glucose (7.7 vs. 7.3 mmol/l;  $P = 0.233$ ) versus the PRANDIAL group.

**CONCLUSIONS** — Treating diabetic survivors of AMI with prandial versus basal strategies achieved differences in fasting blood glucose, less-than-expected differences in postprandial blood glucose, similar levels of A1C, and no difference in risk for future cardiovascular event rates.

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See accompanying editorial, p. 521.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in individuals with diabetes, for which ~65% of deaths are attributable to heart disease or stroke (1,2). Among individuals with type 2 diabetes, those with a previous myocardial infarction have a particularly high risk of additional cardiovascular events (3).

The higher prevalence of classic cardiovascular risk factors in type 2 diabetes only partly explains the increased cardiovascular risk associated with diabetes (2,3). Chronic hyperglycemia increases this risk (4–7) and postchallenge/postprandial hyperglycemia has been associated with CVD independent of A1C or fasting blood glucose (FBG) (8,9). Increased oxidative stress has been suggested as a pathophysiologic mechanism to explain this relationship (10). Furthermore, acarbose, an  $\alpha$ -glucosidase inhibitor that specifically reduces postprandial hyperglycemia, reduced cardiovascular mortality in a diabetes prevention trial (11).

The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial (12) demonstrated a reduction in mortality in patients with type 2 diabetes and recent acute myocardial infarction (AMI) after intensive insulin treatment, and this study was developed to determine the impact of postprandial hyperglycemia on CVD in a similar high-risk population. Thus, the primary objective of the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) study was to demonstrate a difference between two insulin strategies, one targeting postprandial hyperglycemia and the other targeting fasting and interprandial hyperglycemia, on time until the first combined adjudicated cardiovascular event (primary outcome defined as cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for acute coronary syndrome).

**RESEARCH DESIGN AND METHODS**

HEART2D was a prospective, open-label, randomized, two-arm parallel, clinical trial conducted at 105 study centers in 17 countries. The ethical review boards of participating centers approved the protocol and informed consent document. Patients gave written informed consent to participate in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The treatment group assignments were blinded to the sponsor during the trial. The first patient visit occurred on 25 October 2002, and the last patient was enrolled on 6 July 2005.

Study design and methodologies have been described previously (13). In brief, patients (aged 30–75 years) with type 2 diabetes (duration of  $\geq 3$  months and not well controlled with diet therapy alone nor treated with an intensive insulin regimen) entered the trial within 18 days of an AMI (without severe myocardial damage). Within 21 days of hospital admission for the recent AMI, patients were randomly assigned to one of two treatment groups: 1) the PRANDIAL strategy that targeted control of postprandial glycemia with administration of mealtime, thrice-daily insulin lispro (Humalog, Eli Lilly and Company, Indianapolis, IN) or 2) the BASAL strategy that targeted fasting/interprandial glycemia with administration of NPH (Humulin, Eli Lilly and Company) twice daily or insulin glargine (Lantus, sanofi-aventis, Paris, France) once daily. Oral antihyperglycemic agents were discontinued. Both treatments targeted an A1C  $< 7.0\%$ , and the PRANDIAL group had a self-monitored postprandial blood glucose target of  $< 7.5$  mmol/l, whereas the BASAL group had an FBG/premeal blood glucose target of  $< 6.7$  mmol/l. When the A1C was  $> 8.0\%$  on two consecutive visits despite meeting two-thirds of the strategy blood glucose targets, the PRANDIAL treatment was intensified by adding NPH at bedtime, and the BASAL treatment was replaced with twice-daily biphasic intermediate-acting insulin (human insulin 30/70). Patients were to be followed beyond the primary end point and for up to 7 years.

A 10-member blinded adjudication board evaluated all reported primary outcomes, any death, and all cardiovascular secondary outcomes according to predefined criteria. Outcomes were not considered serious adverse events (SAEs) unless they were related to a study drug, study procedure, or study device. If

the SAE was also a study outcome, then the SAE was only in the opinion of the investigator.

**Determination of sample size**

The details of the study sample size determination were published previously (14). In summary, to achieve 80% power, 490 patients must have experienced one of the primary combined outcomes to detect a difference between groups assuming the following: a difference of 2.5 mmol/l between groups in postprandial blood glucose (translates into an 18.5% reduction in the 2-year incidence rate of outcomes), 18 months for patient recruitment, 18 months of patient follow-up after the last randomly assigned patient, 10% annual dropout rate, a 2-year outcomes incidence rate of at least 40% for patients in the least efficacious therapy strategy, and a nominal two-sided significance level of 0.045. Therefore, 1,355 patients were planned for random assignment with 678 patients in each group. The randomization scheme used a minimization technique to ensure balance of disease severity across therapy strategies by accounting for study center, left ventricular ejection fraction (LVEF) ( $\leq 50\%$ ,  $> 50\%$ ), parenteral administration of insulin within the first 24 h in the coronary care unit, and planned angiography.

**Statistical methods**

Unless otherwise noted, statistical analyses were performed for the intent-to-treat population that included all randomly assigned patients who took at least one dose of the study drug. All comparisons were performed using two-tailed tests with a nominal significance level of 0.05. All confidence intervals were computed as two-tailed using 95% coverage. Unless otherwise noted, descriptive statistics are reported as means  $\pm$  SD. Categorical variables are reported as frequencies and proportions.

The time-to-event measures analysis used the number of days from randomization to the first observed cardiovascular event for each patient. Comparisons were performed using a two-sided log-rank test. The hazard ratio (HR) was calculated as the hazard for the PRANDIAL group relative to that of the BASAL group.

During the study, measures of A1C, self-monitored blood glucose, lipids, albumin-to-creatinine ratio, LVEF, and vital signs were analyzed using a pattern mixed model for repeated measures. The model included effects for treatment,

baseline measure, randomization factors, and an additional factor for pattern (defined as  $\leq 30$ ,  $> 30$  and  $\leq 42$ , and  $> 42$  months).

Measures of insulin dose and body weight were analyzed as the end point value using last observation carried forward for each patient. Comparisons for continuous variables were performed using an ANCOVA model incorporating fixed effects for strategy, baseline, and randomization factors. Hypoglycemia rate was analyzed using a nonparametric test of rank data, and all other continuous measures were analyzed as parametric tests. Comparisons for categorical variables were performed using a Pearson's  $\chi^2$  test.

Treatment-emergent adverse events included all new events observed and those preexisting conditions that increased in severity after randomization.

Four interim analyses were performed when 20, 28, 53, and 67% of the events were observed. An external group conducted the analyses that were reviewed by an external data monitoring committee. The first three assessed the effectiveness of glycemic management to targets, safety, and evaluated treatment effects warranting early study termination. The last analysis included an additional guideline for evaluating study futility at a cutoff of 40% for conditional power assuming the trend observed in the interim. Significance levels of 0.001 and 0.0085 were used for all interim analyses to assess superiority and inferiority, respectively, of the PRANDIAL group.

**RESULTS****Patient disposition**

A total of 1,227 patients were enrolled in the study (supplemental Fig. 1, available in an online appendix at <http://dx.doi.org/10.2337/dc08-1671>). Of these, 1,115 patients were randomly assigned and took at least one dose of the study drug (PRANDIAL  $n = 557$ ; BASAL  $n = 558$ ). From this group, 723 (64.8%) were from Central or Eastern Europe (Croatia, Czech Republic, Hungary, Poland, Romania, Russian Federation, Slovakia, and Slovenia), 84 (7.5%) were from Western Europe (Germany, Spain, and the U.K.) or Canada, 149 (13.4%) were from Western Asia (Israel, Lebanon, and Turkey), 70 (6.3%) were from India, and 89 (8.0%) were from South Africa. In the PRANDIAL group, 338 completed the study compared with 346 for the BASAL group. Fifty-one deaths oc-

**Table 1—Baseline characteristics of the intent to treat study population by treatment group**

Variable	PRANDIAL	BASAL	P value
n	557	558	
Sex			0.680
Female	201 (36.1)	208 (37.3)	
Male	356 (63.9)	350 (62.7)	
Age (years)			
Mean	61.1 ± 9.7	60.9 ± 9.8	0.724
Aged ≥65	202 (36.3)	220 (39.4)	0.277
Origin			0.302
Caucasian	484 (86.9)	483 (86.6)	
Western Asian	61 (11.0)	58 (10.4)	
African descent	1 (0.2)	6 (1.1)	
Other	11 (2.0)	11 (2.0)	
Country			>0.999
Duration of diabetes (years)	9.3 ± 7.2	9.0 ± 7.3	0.518
Current tobacco use*	93 (16.7)	81 (14.5)	0.316
Past tobacco use (years)*	13.7 ± 16.5	12.3 ± 15.4	0.143
Weight (kg)	81.12 ± 15.17	81.86 ± 15.86	0.513
BMI (kg/m <sup>2</sup> )	29.0 ± 4.6	29.2 ± 5.0	0.380
Overweight (BMI ≥25 kg/m <sup>2</sup> )	449 (80.8)	447 (80.3)	0.832
Systolic blood pressure (mmHg)	126.88 ± 16.63	127.76 ± 17.75	0.346
Diastolic blood pressure (mmHg)	76.60 ± 9.06	76.87 ± 9.56	0.542
Prior myocardial infarction*	99 (17.8)	101 (18.1)	0.858
Thrombolysis (recent AMI)*	97 (17.4)	98 (17.6)	0.970
Intravenous insulin infusion (recent AMI)	160 (28.8)	160 (28.8)	0.807
A1C (%)	8.42 ± 1.40	8.27 ± 1.52	0.089
Triglycerides (mmol/l)	1.89 ± 1.15	1.77 ± 0.95	0.074
Total cholesterol (mmol/l)	4.45 ± 1.25	4.45 ± 1.25	0.871
HDL cholesterol (mmol/l)	0.96 ± 0.25	0.96 ± 0.23	0.607
LDL cholesterol (mmol/l)	2.68 ± 1.02	2.71 ± 1.02	0.556
Urinary albumin-to-creatinine ratio (mg/g)	115 ± 430	163 ± 610	0.171
QTc interval (ms)	435 ± 33	434 ± 34	0.428
LVEF (%)	50.54 ± 10.05	50.97 ± 10.08	0.829

Data are mean ± SD or n (%). \*Unknown <1.5%.

occurred in each group. Of those patients who were discontinued before cessation of the protocol, 38 in the PRANDIAL group versus 44 in the BASAL group had experienced a primary outcome.

### Baseline characteristics

The PRANDIAL and BASAL groups were similar in age, sex, origin, country, BMI, and duration of diabetes as well as in other clinically relevant measures (Table 1). In addition, both groups were similar in prior historical CVD diagnoses (e.g., prior myocardial infarction and stroke) and with regard to interventions received to open occluded coronary vessels for their most recent AMI. There were no differences in diabetes therapies at baseline between treatment groups (supplemental Table 1, available in an online appendix). Nine percent of patients were managed with diet and exercise. The most common oral agents used were sulfonylureas (26%) and sulfonylureas plus metformin

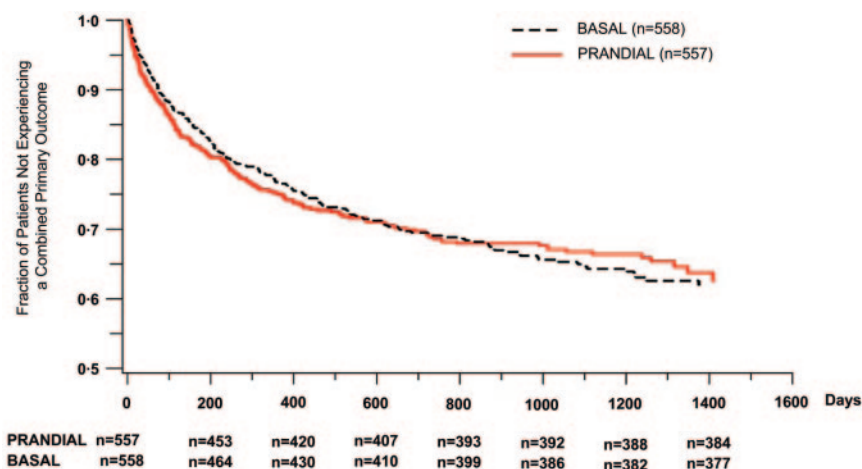
(15%), and 22% of patients used basal/premixed insulin once or twice daily. Other insulin regimens included basal/premixed insulin plus combination oral

therapy (7%) and combination multiple daily injection (≥3 injections/day) (6%).

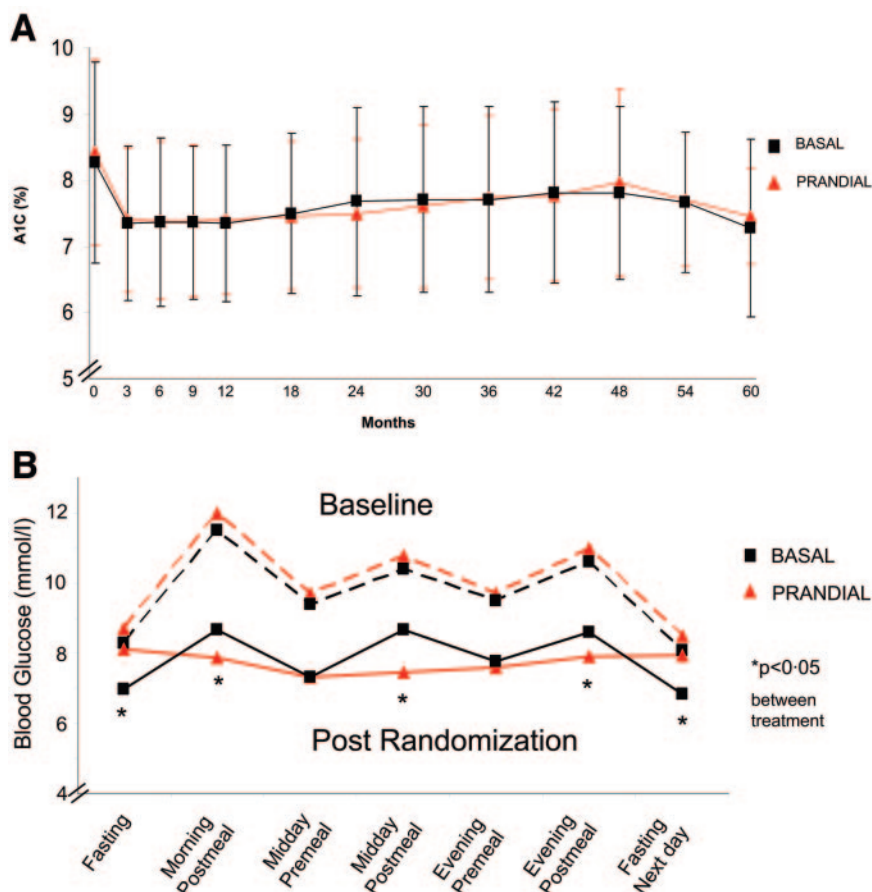
### Primary and secondary cardiovascular end points

The Data Monitoring Committee recommended stopping the trial because of futility on 7 June 2007 after the fourth interim analysis. The sponsor requested that all active patients be brought in for a final visit and the last patient visit was 26 October 2007.

The mean number of days patients participated in the trial after randomization was 963 (2.7 years) (1–1,687 days). The number of PRANDIAL group patients experiencing a first combined adjudicated cardiovascular event was similar to that in the BASAL group ( $n = 174$  [31.2%] vs.  $n = 181$  [32.4%]; HR 0.98 [95% CI 0.8–1.21]) (Fig. 1). Of the 51 deaths in each group, 44 cardiovascular deaths and 3 fatal strokes occurred in the PRANDIAL group compared with 42 cardiovascular deaths and 2 fatal strokes in the BASAL group. The estimated HR for individual cardiovascular events (supplemental Table 2, available in an online appendix), combined events (alternatives to the primary end point) (supplemental Table 3, available in an online appendix), or combined events for those patients achieving targeted blood glucose goals (supplemental Table 4, available in an online appendix) did not reach statistical significance. The estimated HR for post hoc analyses for time to first primary outcome also failed to approach statistical significance for subpopulations (those achieving A1C <7%, A1C ≥7%, optimal blood glucose target values, borderline blood glucose target values, and nonopti-



**Figure 1—**Fraction of patients who did not experience a first primary (combined cardiovascular) adjudicated outcome versus days in trial by treatment strategy (PRANDIAL versus BASAL).



**Figure 2**—Glycemic measures. A: Mean  $\pm$  SD A1C at each visit by treatment strategy (PRANDIAL versus BASAL). B: Seven-point mean self-monitored blood glucose profiles at baseline (dotted line) and throughout the study (postrandomization, solid line) by treatment strategy (PRANDIAL versus BASAL).

mal blood glucose target values) and with Cox regression model adjustments for baseline glycemia and glycemic exposure (data not shown).

### Glycemic measures

A1C did not differ between the PRANDIAL and BASAL groups (mean  $\pm$  SEM  $7.7 \pm 0.1$  vs.  $7.8 \pm 0.1\%$ ;  $P = 0.4$ ) during the study. The A1C values at each visit throughout the study and at the end point (last observation carried forward) were evaluated (Fig. 2A). At the end point, 28% of PRANDIAL group patients achieved an A1C  $<7.0\%$  versus 31% of BASAL group patients ( $P = 0.236$ ) (A1C  $<8.0\%$ : PRANDIAL 63% and BASAL 61%;  $P = 0.375$ ).

The self-monitored blood glucose profiles (Fig. 2B) resulted in a daily mean  $\pm$  SEM over the course of the study for 2-h postprandial blood glucose of  $7.8 \pm 0.3$  versus  $8.6 \pm 0.2$  mmol/l ( $P < 0.01$ ) and postprandial blood glucose excursion of  $0.1 \pm 0.2$  versus  $1.3 \pm 0.1$

mmol/l ( $P < 0.001$ ) for the PRANDIAL and BASAL groups, respectively. Similarly, FBG was  $8.1 \pm 0.2$  versus  $7.0 \pm 0.2$  mmol/l ( $P < 0.001$ ) and daily mean FBG/premeal blood glucose was  $7.7 \pm 0.2$  versus  $7.3 \pm 0.2$  mmol/l ( $P = 0.233$ ) for the PRANDIAL and BASAL groups, respectively. Approximately 47% of patients in the PRANDIAL group achieved the blood glucose target of  $<7.5$  mmol/l for daily mean postprandial blood glucose, and 46% in the BASAL group achieved daily mean FBG/premeal blood glucose  $<6.7$  mmol/l.

### Cardiovascular risk factors and medications

Lipids were similar between groups (PRANDIAL versus BASAL) throughout the course of the study: triglycerides  $2.21 \pm 0.16$  vs.  $2.18 \pm 0.16$  mmol/l ( $P = 0.894$ ); total cholesterol  $4.65 \pm 0.11$  vs.  $4.65 \pm 0.11$  mmol/l ( $P = 0.997$ ); HDL cholesterol  $1.14 \pm 0.02$  vs.  $1.11 \pm 0.02$  mmol/l ( $P = 0.523$ ); and LDL cholesterol

$2.65 \pm 0.09$  vs.  $2.70 \pm 0.09$  mmol/l ( $P = 0.719$ ).

Blood pressure was similar between groups (PRANDIAL versus BASAL) for both systolic ( $131.8 \pm 1.7$  vs.  $132.4 \pm 1.6$  mmHg;  $P = 0.782$ ) and diastolic pressures ( $77.4 \pm 0.9$  vs.  $77.5 \pm 0.9$  mmHg;  $P = 0.978$ ). In addition, heart rate ( $71.4 \pm 1.0$  vs.  $71.1 \pm 1.0$  beats/min;  $P = 0.817$ ), LVEF ( $54.3 \pm 1.30$  vs.  $52.39 \pm 1.22\%$ ;  $P = 0.257$ ), and corrected QT interval ( $423.8 \pm 3.43$  vs.  $424.1 \pm 2.91$  ms;  $P = 0.952$ ) were also similar.

The frequency of concomitant cardiovascular drug use was high and similar between groups (PRANDIAL versus BASAL: 95.0 vs. 95.9%;  $P = 0.478$ ). With the exception of  $\beta$ -blockers (PRANDIAL versus BASAL: 83.7 vs. 78.9%;  $P = 0.046$ ), the other most frequent cardiovascular medications were used similarly between groups: ACE inhibitors or angiotensin receptor blockers (86.3%), statins (76.4%), and aspirin (88.1%).

### Body weight and insulin doses

At the end point, the PRANDIAL compared with the BASAL group gained slightly more weight ( $4.8 \pm 8.0$  vs.  $3.1 \pm 7.1$  kg;  $P < 0.001$ ) and received a greater insulin dose ( $0.60 \pm 0.39$  vs.  $0.52 \pm 0.35$  units/kg;  $P < 0.001$ ). Regimen intensification occurred more frequently in the PRANDIAL group (28%) versus the BASAL group (21%) ( $P = 0.005$ ).

### Safety: hypoglycemia and adverse events

The incidence of hypoglycemia (all) was similar between groups through visit 8 (when this information was collected) (PRANDIAL versus BASAL: 55.3 vs. 55.2%;  $P = 0.367$ ), and the incidence of severe hypoglycemia was also similar throughout the trial (PRANDIAL versus BASAL: 12.9 vs. 9.5%;  $P = 0.071$ ). The incidence of nocturnal hypoglycemia (through visit 8), however, was greater in the BASAL group than in the PRANDIAL group (10.6 vs. 6.1%;  $P = 0.007$ ).

Irrespective of treatment, adverse events were reported by 63.6% of patients overall: 366 patients (65.7%) and 343 patients (61.5%) in the PRANDIAL and BASAL groups, respectively. The three most common adverse events overall (Medical Dictionary for Regulatory Activities preferred terms) were nasopharyngitis (6.5%), hypertension (4.9%), and peripheral edema (4.6%). A significant treatment difference was noted for cardiac failure, with patients in the PRANDIAL

group experiencing more cardiac failure than those in the BASAL group (2.3 vs. 0.7%, respectively;  $P = 0.030$ ); however, congestive cardiac failure occurred similarly (2.2 vs. 2.3%;  $P > 0.999$ ), and, thus, there was no difference between strategies when the categories were combined.

SAEs were reported in 289 patients (25.9%) overall: 144 (25.9%) and 145 (26.0%) in the PRANDIAL and BASAL groups, respectively. The four most common SAEs, irrespective of treatment group, were congestive cardiac failure (1.5%), hypoglycemia (1.3%), pneumonia (1.1%), and chest pain (1.1%). A significant treatment difference was noted in the incidence of sepsis ( $P = 0.038$ ), with more events in the PRANDIAL group relative to the BASAL group (5 vs. 0, respectively).

**CONCLUSIONS**— HEART2D is the first study to examine the effect of a reduction in postprandial glucose on cardiovascular mortality and morbidity. Interim analysis demonstrated no difference between PRANDIAL and BASAL treatments with respect to risk for the first combined adjudicated cardiovascular event in type 2 diabetic patients with a recent AMI, and the trial was halted for statistical futility under advice of the Data Monitoring Committee. Essentially similar overall glycemic control, measured by A1C, was achieved in both treatment arms of the trial, but the PRANDIAL group had consistently lower postprandial glycemia compared with the BASAL group, and the latter had consistently lower fasting glycemia.

There is strong epidemiological evidence that postchallenge/postprandial plasma glucose levels independently predict CVD events, and evidence that fasting plasma glucose levels are predictive is much weaker (8,9). These facts imply that targets for A1C and postprandial glucose levels are important to achieve, not only to reduce the risk of microvascular complications, but also to reduce the risk of CVD morbidity and mortality in individuals with diabetes.

Postprandial hyperglycemia has been associated with increased oxidative stress, inflammation, endothelial dysfunction, decreased fibrinolysis, plaque instability, and cardiac events (10). A direct and proportional association exists between postprandial hyperglycemia and both coronary artery disease and cardiac events. The postprandial hyperglycemia hypothesis has been supported by inter-

ventional studies demonstrating that reduced postprandial glycemia and lipids decrease inflammation and improve endothelial function (15) and are associated with a lesser degree of atherosclerotic progression (14,16,17). The HEART2D study succeeded in creating two groups with comparable A1C levels and similar proportions of patients achieving blood glucose targets, despite clear differences between postprandial glucose and fasting glucose. More importantly, however, the A1C values did not reach the goal of  $<7.0\%$ . Perhaps there may have been reluctance to intensively optimize glycemia in a population with a high risk for a cardiovascular event. In addition, neither a 2.5 mmol/l difference in postprandial glycemia between groups nor the 40% event rate was achieved as assumed for the power calculations.

The DIGAMI trial (12), which included both type 1 and type 2 diabetic patients with recent AMI, demonstrated at 1 year of follow-up a significant reduction in mortality between groups and an  $\sim 0.5\%$  separation in A1C. A similar separation in glycemic control was noted in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study (18), in which the primary composite cardiovascular end point failed to reach significance between therapies, but the secondary composite end point did reach significance.

On the other hand, the subsequent DIGAMI-2 study (19) failed to establish any glycemic separation between treatment groups, and no difference was noted in cardiovascular outcomes. It has been speculated that the results of the two DIGAMI trials may have been explained by glycemic exposure during chronic diabetes care as opposed to the acute glycemic intervention (20). It is significant that the recent results of three large, well-designed clinical trials of glycemic interventions to improve cardiovascular outcomes in type 2 diabetes failed to provide conclusive results. The Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) trial (21) demonstrated increased mortality with intensive glycemic goals (A1C of 6.4%), the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trial (22) showed similar cardiovascular outcomes with similarly achieved intensive glycemic goals, and the VA Diabetes Trial (VADT) (23) results demonstrated that patients with a shorter duration of type 2 diabetes

may obtain cardiovascular benefit with intensive control, but diabetic patients with a longer duration of type 2 diabetes may experience greater risk for adverse outcomes with intensive glycemic goals. Although the mean glycemic exposure as measured by A1C in HEART2D may have been similar to that with the standard therapies in these trials, post hoc analysis based on overall glycemic exposure (A1C) produced the same results as the primary analysis.

The null results of HEART2D may be explained by the advanced state of CVD in the patients studied. Retarding the progression of advanced atherosclerosis may be very difficult, similar to observations with advanced microvascular complications. Many cardiovascular events occurred early in the course of HEART2D, indicating extension or progression of preexisting disease. Recent studies differ from DIGAMI and suggest that lower levels of glycemia and postprandial hyperglycemia with or without a previous cardiovascular event may require many years to produce favorable effects on cardiovascular events (5,21–24). Furthermore, the effects of other risk factor reduction (hypertension and lipids, especially LDL), which were similar between the groups, may be greater than glycemia on cardiovascular outcomes. Of note, the use of concomitant cardiovascular medical therapy was more prevalent (e.g., aspirin, statins, and ACE inhibitors) in HEART2D than in DIGAMI. Therefore, correcting risk factors with cardiovascular medications and improved technical interventions (compared with DIGAMI) during the course of this trial may have obscured the effect of glycemic intervention on cardiovascular outcomes. Some of these therapies may also counterbalance the adverse effects of postprandial glucose on oxidative stress (25). In addition, the difference in glycemic control achieved between the groups was more modest than had been predicted at the start of the clinical trial. Greater separation in postprandial blood glucose (the goal was 2.5 mmol/l postprandial blood glucose difference between strategies) than that observed in HEART2D may be needed to adequately test the hypothesis. Moreover, overall glycemic goals were not fully realized, and a lower A1C level or a much larger sample size may be needed to distinguish between components of the diurnal glucose profile.

The HEART2D study implemented strategies to target either fasting/premeal

or postprandial blood glucose control in patients with type 2 diabetes who had survived a myocardial infarction. Modest differences in postprandial and fasting blood glucose were achieved during the study, but relatively similar A1C levels were obtained with both treatment strategies. The magnitude of the differences in postprandial glycemia was less than expected, and the risk of CVD outcomes was similar between the treatment groups.

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## References

1. Stamler J, Vaccaro O, Neaton JD, et al.: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
2. Haffner SM, Lehto S, Ronnema T, et al.: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
3. Eberly LE, Cohen JD, Prineas R, et al.: Impact of diabetes and incident nonfatal cardiovascular disease on 18-year mortality. *Diabetes Care* 26:848–854, 2003
4. Stratton IM, Adler AI, Neil HA, et al.: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
5. Holman RR, Paul SK, Bethel MA, et al.: 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359:1577–1589, 2008
6. Beckman JA, Creager MA, Libby P: Diabetes and atherosclerosis: epidemiology, pathophysiology and management. *JAMA* 287:2570–2581, 2002
7. Lakka HM, Laaksonen DE, Lakka TA, et al.: Metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288:2709–2716, 2002
8. DECODE: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 161:397–405, 2001
9. Meigs JB, Nathan DM, D'Agostino RB Sr, et al.: Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. *Diabetes Care* 25:1845–1850, 2002
10. Ceriello A: Postprandial hyperglycemia and diabetes complications: is it time to treat? *Diabetes* 54:1–7, 2005
11. Chiasson JL, Josse RG, Gomis R, et al.: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 290:486–494, 2003
12. Malmberg K: Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus: DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ* 314:1512–1515, 1997
13. Milicevic Z, Raz I, Strojek K, et al.: Hyperglycemia and its effect after acute myocardial infarction on cardiovascular outcomes in patients with type 2 diabetes mellitus (HEART2D) study design. *J Diabetes Complications* 19:80–87, 2005
14. Esposito K, Giugliano D, Nappo F, et al.: Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation* 110:214–219, 2004
15. Shimabukuro M, Chinen I, Higa N, et al.: Effects of dietary composition on postprandial endothelial function and adiponectin concentrations in healthy humans: a crossover controlled study. *Am J Clin Nutr* 86:923–928, 2007
16. Mita T, Watada H, Shimizu T, et al.: Nateglinide reduces carotid intima-media thickening in type 2 diabetic patients under good glycemic control. *Arterioscler Thromb Vasc Biol* 27:2456–2462, 2007
17. Alsema M, Schindhelm RK, Dekker JM, et al.: Postprandial glucose and not triglyceride concentrations are associated with carotid intima media thickness in women with normal glucose metabolism: the Hoorn prandial study. *Atherosclerosis* 196:712–719, 2008
18. Dormandy JA, Charbonnel B, Eckland DJ, et al.: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 366:1279–1289, 2005
19. Malmberg K, Ryden L, Wedel H, et al.: Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 26:650–661, 2005
20. Van den Berghe G: Insulin vs. strict blood glucose control to achieve a survival benefit after AMI? *Eur Heart J* 26:639–641, 2005
21. The Action to Control Cardiovascular Risk in Diabetes Study Group: Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358:2545–2559, 2008
22. The ADVANCE Collaborative Group: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 358:2560–2572, 2008
23. Duckworth W, Abraira C, Moritz T, et al.: Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 360:129–139, 2009
24. Juutilainen A, Lehto S, Ronnema T, et al.: Similarity of the impact of type 1 and type 2 diabetes on cardiovascular mortality in middle-aged subjects. *Diabetes Care* 31:714–719, 2008
25. Ceriello A, Assaloni R, Da Ros R, et al.: Effect of atorvastatin and irbesartan, alone and in combination, on postprandial endothelial dysfunction, oxidative stress, and inflammation in type 2 diabetic patients. *Circulation* 111:2518–2524, 2005