Post Hoc Subgroup Analysis of the HEART2D Trial Demonstrates Lower Cardiovascular Risk in Older Patients Targeting Postprandial Versus Fasting/Premeal Glycemia

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OBJECTIVE—To identify the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) trial subgroups with treatment difference.

RESEARCH DESIGN AND METHODS—In 1,115 type 2 diabetic patients who had suffered from an acute myocardial infarction (AMI), the HEART2D trial compared two insulin strategies targeting postprandial or fasting/premeal glycemia on time until first cardiovascular event (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for acute coronary syndrome). The HEART2D trial ended prematurely for futility. We used the classification and regression tree (CART) to identify baseline subgroups with potential treatment differences.

RESULTS—CART estimated the age of >65.7 years to best predict the difference in time to first event. In the subgroup aged >65.7 years (prandial, n = 189; basal, n = 210), prandial patients had a significantly longer time to first event and a lower proportion experienced a first event (n = 56 [29.6%] vs. n = 85 [40.5%]; hazard ratio 0.69 [95% CI 0.49–0.96]; P = 0.029), despite similar A1C levels.

CONCLUSIONS—Older type 2 diabetic AMI survivors may have a lower risk for a subsequent cardiovascular event with insulin targeting postprandial versus fasting/premeal glycemia.

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The primary objective of the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) trial was to assess the time to first cardiovascular event for two glucose-lowering strategies in type 2 diabetic patients who had survived an acute myocardial infarction (AMI) (1). The trial was stopped early for futility, partly because of fewer than expected cardiovascular events.

We conducted post hoc analyses using the classification and regression tree (CART) technique (2) to determine patient subgroups for which the two strategies differed in time to first cardiovascular event. CART sifts through numerous covariates to determine which covariate, and at what cut point, best splits the data.

RESEARCH DESIGN AND METHODS

—Details of the HEART2D trial have been previously published (1). The primary outcome of time to first combined adjudicated cardiovascular event (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for acute coronary syndrome) was compared in 1,115 type 2 diabetic patients after an AMI hospital admission. Patients were randomly assigned to prandial glycemia control (thrice-daily insulin lispro) or fasting/premeal glycemia control (twice-daily NPH or once-daily insulin glargine) (1) and participated a mean of 2.7 years post–randomization assignment.

CART estimated the best subgroup with respect to difference in primary outcome. Decision trees in each arm used a "time to cardiovascular event" target and 45 covariate predictors based on baseline demographics and clinical characteristics. A 10-fold crossvalidation technique determined the right-sized tree and built a model with good generalization prior to testing the subgroups. Previously published statistical analyses (1) were performed to determine treatment differences for the intent-to-treat population. Baseline HDL interactions were tested using a generalized linear model.

RESULTS

—CART produced a one-level decision tree and identified age at the cut point of >65.7 years as the best predictor of time to first cardiovascular event. Among the patients screened (1), 451 comprised the subgroup aged >65.7 years and 52 patients did not continue, resulting in 399 intent-to-treat population patients (prandial, n = 189; basal, n = 210). Ninety-four (49.7%) of the prandial and 91 (43.3%) of the basal patients did not continue, and 214 patients completed the trial (prandial, n = 95 [50.3%]; basal, n = 119 [56.7%]).

There were no significant differences in baseline characteristics between arms,

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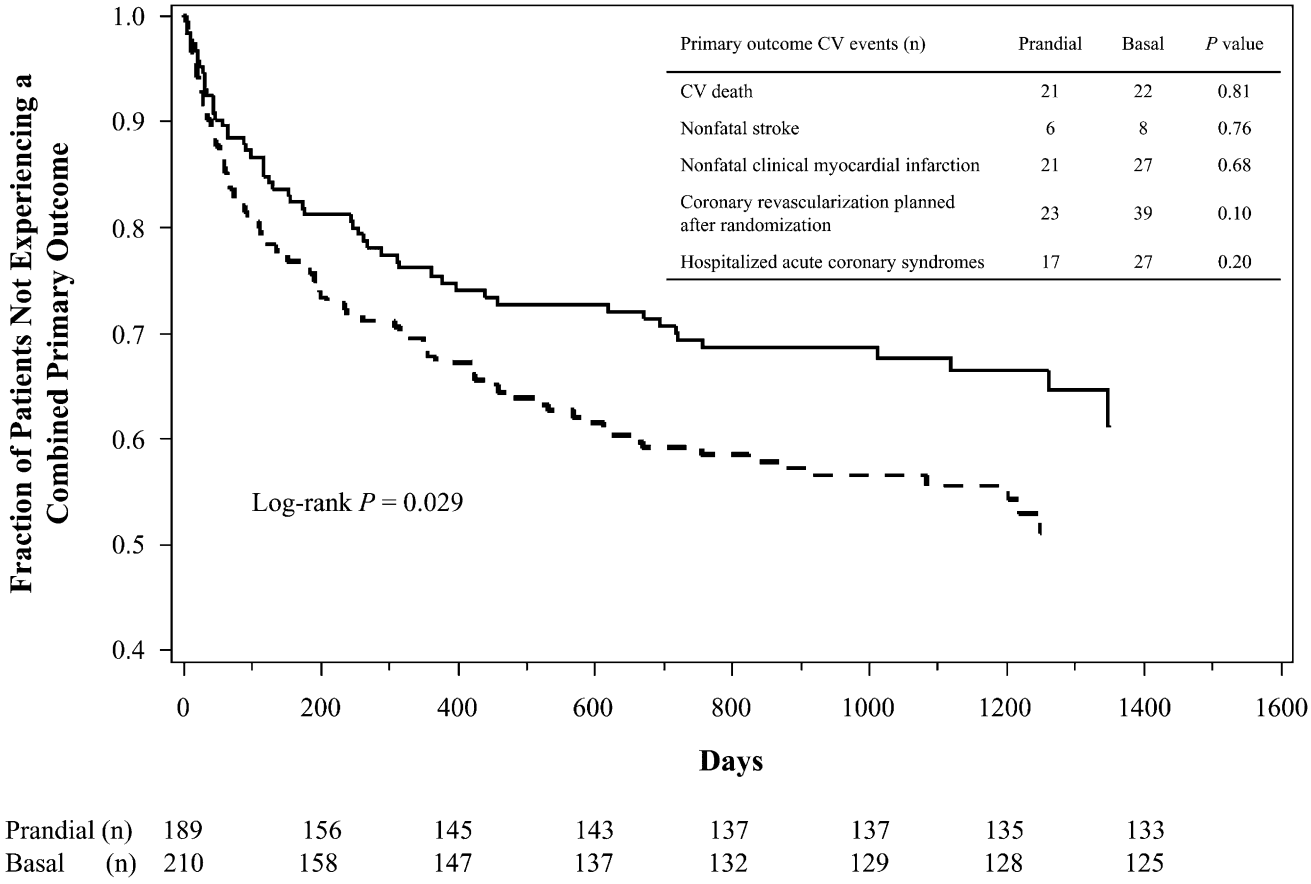
including A1C, diabetes therapies, prior cardiovascular disease history, or other clinically relevant measures, but HDL cholesterol levels were significantly higher with the prandial control (means 1.0 ± 0.3 vs. 1.0 ± 0.2 mmol/L; medians 1.0 ± 0.3 vs. 0.9 ± 0.2 mmol/L; $P = 0.013$).

In the subgroup aged >65.7 years, prandial arm patients experienced a significantly lower time to first cardiovascular event (Fig. 1), and a significantly lower proportion experienced a first cardiovascular event ($n = 56$ [29.6%] vs. $n = 85$ [40.5%]; hazard ratio 0.69 [95% CI 0.49–0.96]; $P = 0.029$). Risk for individual cardiovascular events comprising the primary outcome did not differ significantly between arms (Fig. 1). The effect of baseline HDL prior to the index event was not statistically significant for the primary outcome. The hazard ratio for all-cause death, cardiovascular death, or other analyses did not reach statistical significance. In the subgroup aged ≤65.7 years, arms did not differ significantly for the primary outcome ($n = 118$ [32.1%] vs. $n = 96$ [27.6%]; 1.24 [0.95–1.63]; $P = 0.11$).

There were no differences in overall glycemia or in combined measures of premeal or postprandial glycemia. Mean morning premeal blood glucose value was significantly lower with the basal arm (7.87 ± 0.32 vs. 6.71 ± 0.22 mmol/L; $P = 0.001$), and 2-h postprandial blood glucose excursion was significantly lower with prandial control (0.17 ± 0.24 vs. 1.21 ± 0.15 mmol/L; $P < 0.0001$) because of significantly lower morning and noon excursions. Nocturnal hypoglycemia rates were significantly higher in the basal arm ([means ± SEM] 0.15 ± 0.04 vs. 0.61 ± 0.10 per patient per episode per year; $P < 0.001$), whereas overall and severe hypoglycemia rates and total insulin dose did not differ significantly. BMI was significantly higher in the prandial arm (30.08 ± 0.29 vs. 29.21 ± 0.27 kg/m^2; $P = 0.015$), but lipid profiles, blood pressure levels, left ventricular ejection fraction, and QTc interval were not.

CONCLUSIONS—The premise of the HEART2D trial was that the two major A1C components, prandial and fasting/premeal glycemia, may affect cardiovascular risk differently (3). Recent trials (4–6) demonstrated that intensive glucose therapy lowered A1C but with no significant difference in major cardiovascular events. Although a meta-analysis (7) reported a modest effect of total glycemic exposure on cardiovascular risk, older-patient-subgroup reports demonstrated no significant effect (4,5,7). This HEART2D post hoc analysis using CART demonstrated that older (aged >65.7 years) AMI survivors with type 2 diabetes may have a lower risk for subsequent cardiovascular events with insulin therapy targeting prandial versus fasting/premeal glycemia, despite similar A1C.

Older patients may be susceptible to glycemic and nonglycemic mechanisms



Primary outcome CV events (n)	Prandial	Basal	*P* value
CV death	21	22	0.81
Nonfatal stroke	6	8	0.76
Nonfatal clinical myocardial infarction	21	27	0.68
Coronary revascularization planned after randomization	23	39	0.10
Hospitalized acute coronary syndromes	17	27	0.20

Figure 1—*Kaplan-Meier survival curve of the percentage of HEART2D patients in the subgroup aged >65.7 years who did not experience a first combined adjudicated cardiovascular (CV) event (defined as CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for acute coronary syndrome) vs. days in the trial by insulin strategy. Solid black line, prandial insulin arm (targeted prandial glycemia control); dashed black line, basal insulin arm (targeted fasting/premeal glycemia).*

associated with the postprandial period, which may increase cardiovascular risk. The more pronounced postprandial excursions in the older-subgroup basal arm may indicate increased exposure to postprandial-state abnormalities of oxidative stress, inflammation, endothelial dysfunction (8,9), a prothrombotic state characterized by elevated platelet and coagulation activation and inhibited fibrinolysis (10,11), and less vasodilation caused by lower insulinemia (12). Abnormalities of sympathetic function, vasoactive peptide action, and meal carbohydrate content may predispose older patients to postprandial hypotension and cardiovascular events (13,14).

On the other hand, the significantly lower fasting blood glucose and significantly greater nocturnal hypoglycemia in the basal versus prandial arm may have contributed to the difference in cardiovascular outcomes. Lower fasting blood glucose and greater nocturnal hypoglycemia in the older subgroup compared with the total HEART2D trial population (1) may explain the disparity between the two analyses.

The major limitation of this analysis is that its post hoc nature with multiple testing on many variables renders it only hypothesis generating. Additional limitations include the fact that the follow-up period may be inadequate to evaluate cardiovascular outcomes, the primary outcome included two subjective outcomes, patients had advanced cardiovascular disease, and dropout was high.

Most people with diabetes in developed countries are aged ≥65 years, and prevalence in that age-group worldwide likely will rise (15). Our finding that prandial glycemia control was associated with lower cardiovascular risk than fasting/premeal glycemia control for older AMI survivors with type 2 diabetes warrants definitive investigation.

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