A Prospective Trial of Risk Factors for Sulfonylurea-Induced Hypoglycemia in Type 2 Diabetes Mellitus

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Context.—Retrospective studies have identified oral sulfonylureas, age, and fasting as major risk factors for hypoglycemia in patients with type 2 diabetes. Sulfonylureas may be withheld from elderly patients out of concern for hypoglycemia.

Objective.—To evaluate the hypoglycemic effects of maximum doses of once-daily second-generation sulfonylureas administered to fasting elderly patients.

Design.—A prospective, randomized, double-blind clinical trial.

Setting.—The University of New Mexico General Clinical Research Center.

Patients.—Fifty-two sulfonylurea-treated subjects with type 2 diabetes with a mean (SD) age of 65.1 (5.7) years.

Interventions.—Subjects were randomly assigned to glyburide or glipizide gastrointestinal therapeutic system (GITS). Each subject participated in three 23-hour fasting studies after the sequential administration of 1 week of placebo and 1 week of 10 mg and 1 week of 20 mg of the assigned sulfonylurea.

Main Outcome Measures.—Occurrence of hypoglycemia (defined as plasma glucose level <3.33 mmol/L [60 mg/dL]) and hormonal parameters during the final 9 hours of the 23-hour fast in patients who had taken sulfonylureas vs placebo.

Results.—No hypoglycemia was observed during 156 fasting studies. Plasma glucose level was decreased (nadir, 4.9 mmol/L [88 mg/dL]) for a 20-mg dose of glyburide vs 8.3 mmol/L [150 mg/dL] for placebo; nadir, 5.8 mmol/L [105 mg/dL] for a 20-mg dose of glipizide GITS vs 8.7 mmol/L [157 mg/dL] for placebo), and serum insulin was increased in the sulfonylurea studies compared with placebo (P < .001). Plasma glucose parameters did not differ between the 2 sulfonylureas, but C peptide concentrations were increased in the glyburide group compared with glipizide GITS in the 20-mg study (P = .05). Concentrations of epinephrine were increased in the sulfonylurea studies compared with placebo (P < .001). Epinephrine secretion increased when glucose concentration fell below the mean (SD) level of 9.10 (2.66) mmol/L (164 [48] mg/dL) in the 10-mg study and 8.77 (2.83) mmol/L (158 [51] mg/dL) in the 20-mg study.

Conclusions.—Fasting was well tolerated among these elderly patients with type 2 diabetes treated with sulfonylureas. Older age should not be considered a contraindication to sulfonylurea treatment for diabetes. Stimulation of epinephrine secretion at normal or elevated plasma glucose levels appears to be the primary mechanism of protection against hypoglycemia in this study.

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DESPITE the availability of new agents for the treatment of type 2 diabetes mellitus, oral sulfonylureas remain a cornerstone of therapy. Sulfonylureas are appealing in the treatment of type 2 diabetes because they are relatively inexpensive and are well tolerated. Hypoglycemia, however, is a major safety concern with the sulfonylureas. Jennings et al showed that up to 20% of patients taking oral sulfonylureas experience symptoms consistent with hypoglycemia over a 6-month period, but hypoglycemia was not corroborated by plasma glucose determination in this study. Moreover, in a comprehensive review of 1418 cases of severe drug-induced hypoglycemia, Seltzer retrospectively identified sulfonylurea ingestion, advanced age, and fasting as the major risk factors for the development of hypoglycemia requiring hospitalization. Specifically, sulfonylurea ingestion was a factor in 65% of adult cases; 86% of cases were older than 50 years, and the omission of 1 or more meals was implicated in 80% of cases. This report is flawed, however, by the lack of a control group, by its inclusion of intentional overdoses, and by its retrospective design. Thus, despite concern over the risk of hypoglycemia associated with sulfonylureas, the role of perceived risk factors in the pathogenesis of hypoglycemia has not been rigorously examined. In fact, avoidance of sulfonylureas out of fear of inducing hypoglycemia may unnecessarily deprive elderly patients with type 2 diabetes of an affordable and effective treatment option.

The recently published interim results of the United Kingdom Prospective Diabetes Study reported severe hypoglycemia occurring at a rate of 0.7% per year among 922 patients newly di-
agonsed as having type 2 diabetes assigned to treatment with sulfonylureas. The cumulative incidence of severe hypoglycemia occurring in this group over the 6 years of the study is reported to be 3.3%, suggesting that approximately 30 episodes of hypoglycemia “requiring medical assistance” were documented. Unfortunately, hypoglycemia was not corroborated by blood glucose determination in this study, and details of the episodes are not provided. Additionally, this study did not specifically focus on elderly patients with type 2 diabetes and did not exclude patients who were abusing alcohol or using other drugs that have been associated with hypoglycemia. Interestingly, an incidence of severe hypoglycemia of 0.05% per year was reported among patients who were treated with diet alone. This raises questions about the cause of these episodes and reinforces the importance of care- taking alcohol or using other drugs that have been associated with hypoglycemia.

Based on the observation that most elderly patients with type 2 diabetes have intact glucose counterregulatory mechanisms, we hypothesized that the development of hypoglycemia would be acceptably low in elderly patients with type 2 diabetes taking maximal doses of once-daily second-generation oral sulfonylurea agents during a short-term fast. This study reports the glucose and hormonal responses of 52 elderly subjects with type 2 diabetes receiving submaximal and maximal doses of once-daily second-generation sulfonylureas during a 23-hour fast compared with placebo. The results suggest that healthy elderly subjects with type 2 diabetes who take sulfonylureas do not develop hypoglycemia during a short-term fast and, further, that such patients may be protected against the development of hypoglycemia by the incremental secretion of epinephrine.

### METHODS

#### Study Subjects

Fifty-eight subjects with type 2 diabetes were enrolled in a sequential, randomized, double-blind, placebo-controlled, 3-week study of 2 different once-daily sulfonylureas (glyburide and glipizide gastrointestinal therapeutic system [GITS]) (Figure 1). Glipizide GITS employs the principle of an osmotic pump to effect a steady release of glipizide from the tablet over 24 hours. Inclusion criteria consisted of type 2 diabetes treated with oral sulfonylureas alone for at least 2 months, an age between 55 and 75 years, a glycosylated hemoglobin level between 0.068 and 0.12 (normal range, 0.040-0.068), and a body mass index (weight in kilograms divided by the square of height in meters) of less than 35 kg/m². Patients were excluded from the study by the presence of severe cardiovascular, gastrointestinal, renal, or hepatic disease, concurrent medications that interfere with glucose homeostasis, malignancy, or substance abuse. Patients were recruited through a combination of database searches and local advertising, and all subjects received compensation for time and expenses for participating in the study. Descriptive characteristics for the participants are summarized in Table 1. All tabular results are expressed as mean (SD), and in the figures, mean and SE are depicted.

Of the 58 subjects who enrolled in the study, 6 subjects dropped out for personal reasons, and 52 completed the protocol. None of the dropouts completed more than the placebo study or experienced hypoglycemia, and these data are not included in the analysis. All participants gave informed consent for the protocol as approved by the University of New Mexico’s Institutional Review Board.

#### Study Protocol

On enrollment, all treatment with diabetes medications was discontinued, and subjects were randomized to receive either glyburide or glipizide GITS during the study. Subjects received 2 sets of study medication each week that were identical in appearance. One set of study medication consisted of placebo and the other contained active drug, except during the first week of the study, when both sets of study medication contained placebo. Patients were instructed to take both medications daily in the morning before breakfast. All subjects were provided with a capillary blood glucose monitor and were instructed to monitor their glucose twice daily and whenever hypoglycemic symptoms occurred. All subjects received placebo for 7 to 9 days, followed by 10 mg of glyburide or glipizide GITS for 7 to 9 days, followed by 20 mg of glyburide or glipizide GITS (maximal dose) for 7 to 9 days. Pharmacologic data indicate that steady-state concentrations of sulfonylureas are achieved within 1 week of therapy.

After 7 to 9 days of each sequential dose, patients were admitted to the University of New Mexico General Clinical Research Center for a 23-hour fasting study. Antecubital intravenous access was established to obtain blood samples, and subjects were fed a 33.5-kJ (8 kcal)/kg American Diabetes Association supper at 1800 on the evening prior to study. No energy-containing food was provided for the next 23 hours. At 0800 the following morning, subjects ingested their final dosage of that week’s medication. Blood was collected for glucose, insulin, C peptide, glucagon, epinephrine, and norepinephrine determinations at 0750 and 0800 (baseline determinations) and then every 30 minutes during the final 9 hours of study. Blood was sampled for serum sulfonylurea concentrations at 0800 on the day of the placebo study and at 0800, 1000, 1200, 1400, 1600, and 1700 during the 2 sulfonylurea studies. Additionally, all subjects completed a 43-item hypoglycemia symptom questionnaire at 0800, 1000, 1200, 1400, 1600, and 1700 during the study period. Symptoms evaluated included drowsiness, hunger, nervousness, blurred vision, weakness, light-headedness, trembling, sweating, palpitations, tachycardia, dyspnea, and difficulty concentrating. Subjects rated each of the symptoms on a scale of 1 to 7 (none to 7 (severe symptoms)). On completion of each study, supper was provided, and the next week’s medication was dispensed.

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<th>Table 1.—Demographic and Descriptive Characteristics of the 52 Subjects With Type 2 Diabetes Studied*</th>
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*Data are mean (SD) unless indicated otherwise. GITS indicates gastrointestinal therapeutic system. P<.05 for all comparisons.
Subjects were allowed free access to non–energy-containing beverages during the fast, and all subjects drank a single caffeinated beverage (coffee or diet cola) at 0800 on the morning of the fast. Furthermore, all subjects participated in a supervised walk around the hospital grounds between 0800 and 0830 to simulate normal activity. The study protocol is summarized in Figure 2.

Study Variables

Development of hypoglycemia during the final 9 hours of the 23-hour fast was the primary study outcome variable. Hypoglycemia was prospectively defined as a plasma glucose level less than 3.33 mmol/L (60 mg/dL) with typical hypoglycemic symptoms or any plasma glucose level less than 2.78 mmol/L (50 mg/dL). Secondary analyses included comparison of plasma glucose, insulin, C peptide, glucagon, and catecholamine concentrations between placebo and the 2 doses of sulfonylurea therapy, as well as between glyburide and glipizide GITS. Summary measures of these parameters that were analyzed include the baseline value (mean of 0750 and 0800 results), the mean value over the entire 9-hour study, and the peak and nadir values during each 9-hour study. Serum sulfonylurea concentrations were analyzed by comparing the 10-mg and 20-mg studies using a repeated-measures analysis of variance (ANOVA) within each treatment group. Additionally, plasma glucose thresholds for the secretion of epinephrine were determined. To summarize the data obtained from the hypoglycemia symptom questionnaire, 14 of the 43 symptoms were profiled by subtracting the baseline score (0800) from the peak score obtained during the subsequent 9 hours of fasting.

Sample Analysis

Plasma glucose concentrations were determined with a glucose oxidase-based analyzer (Beckman Instruments, Fullerton, Calif). Plasma was separated from blood elements by centrifugation immediately after sampling and frozen at –20°C for later determination unless capillary blood glucose values were less than 4.44 mmol/L (80 mg/dL), at which time plasma glucose levels were determined immediately. Serum insulin concentrations were determined using an insulin radioimmunoassay kit (Coat-a-Count, Diagnostic Products Corp, Los Angeles, Calif). For 8 patients who had previously received exogenous insulin (none within 3 months of study), free insulin concentrations were determined after treatment of the serum with 25% polyethylene glycol. C peptide concentrations were determined using radioimmunoassay (INCSTAR, Stillwater, Minn). Serum glucagon concentrations were determined by the core laboratory at Washington University (St Louis, Mo) using radioimmunoassay. Samples for plasma epinephrine and norepinephrine were placed on ice immediately after sampling and stored at –70°C until being assayed radioenzymatically. Plasma samples for sulfonylurea concentration were frozen at –20°C until assay by high-performance liquid chromatography (Hazelton Laboratories, Madison, Wis).12,13

Sample Size and Statistical Analysis

Our original power analysis was based on the rates of hypoglycemia expected to occur with sulfonylurea therapy during a short-term fast, but surprisingly, no hypoglycemia was observed. Accordingly, we performed a post hoc analysis using the plasma glucose nadir as a surrogate variable for our estimate of power. Since the observed common SD in this parameter was 2.22 mmol/L (40 mg/dL), our sample size is adequate to detect a difference between the 2 sulfonylurea preparations and/or between active treatment and placebo therapy of 1.78 mmol/L (32 mg/dL) with 80% power and a P value of .05.

Comparisons for an effect of treatment group (glyburide vs glipizide GITS) as a grouping factor and dosage (placebo vs 10 mg vs 20 mg) as a repeated factor were performed using a repeated-measures ANOVA with the Fisher least significant difference method of post hoc pairwise comparisons using SAS software for the summary measures previously described. Plasma glucose thresholds for epinephrine secretion were determined using a 2-segment piecewise linear model of the individual data from each study. This was accomplished using a modification of the methods of Clutter et al16 by analyzing plasma epinephrine concentrations against the concomitant plasma glucose concentration and deriving the glucose level at which the slope changed from zero. This nonlinear model was implemented with the SAS PROC NLIN program using an intercept, a slope, and a glucose threshold where the slope changed.15

RESULTS

Plasma Glucose and Hypoglycemia

For comparisons within any of the dosages studied, plasma glucose concentrations did not differ between the treatment groups with respect to any of the 4 summary measures (baseline, average, peak, or nadir) by ANOVA. These data are shown in Table 2. As expected, plasma glucose was significantly decreased when comparing active drug treatment with placebo (Figure 3). Additionally, a significant difference was observed between the 10-mg and 20-mg doses for both drugs. No hypoglycemia occurred during any of the 156 studies.

Serum Insulin and C Peptide

As expected, insulin concentrations were increased with sulfonylurea therapy as compared with placebo. Specifically, as shown in Table 2, baseline, mean, peak, and nadir concentrations of insulin were significantly higher than placebo in the glyburide group at both 10-mg and 20-mg doses, but only mean and nadir insulin levels were increased with sulfonylurea treatment in the glipizide GITS group. Baseline levels of C peptide were higher than placebo for the 10-mg dose of glyburide (P<.001) and for the 20-mg dose of both glyburide (P<.001) and glipizide GITS (P<.05). Mean and peak C peptide levels were significantly increased compared with placebo for both treatment groups at the 10-mg and 20-mg doses (Figure 4). Finally, mean C peptide concentrations (a surrogate for endogenous insulin secretion) were increased in the glyburide group compared with the glipizide GITS group during the 20-mg study by nonpaired Student t test (P=.05).

Counterregulatory Hormones

Since there was no effect of treatment group with respect to any of the measured counterregulatory hormones (Table 2), the data are summarized by dosage in Figure 5, with the data from both treatment groups being combined for a given dosage (n=52).

Concentrations of glucagon and norepinephrine did not differ according to treatment group or dosage (Table 2, Figure 5, A and B). There were no differences in plasma epinephrine concentrations according to treatment group in any of the 3 studies. Moreover, baseline and nadir levels of epinephrine did not differ from placebo with active sulfonyl-
Glipizide GITS (n=25)

Serum Sulfonylurea Concentrations

post hoc analysis. There was no difference in epinephrine response between the 10-mg and 20-mg studies.

Glucose Thresholds for Epinephrine Secretion

No glucose threshold for epinephrine secretion could be determined from the placebo study using nonlinear regression. During active sulfonylurea treatment, however, this model derived mean thresholds of 6.2 (3.2) mg/dL during the 10-mg and 20-mg studies when the treatment groups were combined (P<.001). There was no difference in epinephrine response between the 10-mg and 20-mg studies.

Serum Sulfonylurea Concentrations

Serum sulfonylurea levels were below therapeutic (<10 ng/mL) for both glyburide and glipizide GITS after the week of placebo therapy. On average, glipizide concentrations approximately doubled during active sulfonylurea treatment over baseline, while concentrations of glyburide increased approximately 6-fold over baseline after dosing (Figure 6). Serum sulfonylurea concentrations were significantly increased during the 20-mg study compared with those obtained during the 10-mg study for both drugs.

Hypoglycemic Symptom Questionnaire

Study subjects did not differ between treatment group or dosage with respect to any of the 14 hypoglycemia symptom variables (data not shown). In general, symptom scores remained very low throughout the studies, except for hunger, for which scores increased similarly during all 3 studies.

COMMENT

Type 2 diabetes is common in the elderly, with approximately 10% of individuals older than 65 years having a diagnosis of diabetes and another 10% having occult diabetes. An additional 23% of this population meet criteria for impaired glucose tolerance, so 40% to 50% of individuals older than 65 years manifest some abnormality of carbohydrate metabolism. Because the proportion of the American population older than 65 years is projected to increase from the current level of 12% to 22% by the year 2040, the burden of type 2 diabetes will become increasingly prevalent in the near future. As such, the dilemma of how best to care for these patients must be considered. Previous retrospective reports have suggested that long-acting sulfonylureas (such as chlorpropamide and glyburide) are more likely to cause hypoglycemia and should be avoided in elderly patients, but there are insufficient prospective, controlled data to support these claims. Although alternatives to sulfonylurea therapy have recently become available, these agents have the drawbacks of potential adverse gastrointestinal effects (eg, metformin, acarbose) and high cost (eg, metformin, troglitazone, acarbose). Thus, although hypoglycemia remains an appropriate concern for the elderly diabetic patients who use them, sulfonylureas are likely to remain a cornerstone of type 2 diabetes therapy.

This placebo-controlled prospective study demonstrates that hypoglycemia does not normally occur in otherwise healthy individuals older than 65 years having a diagnosis of diabetes and another 10% having occult diabetes. An additional 23% of this population meet criteria for impaired glucose tolerance, so 40% to 50% of individuals older than 65 years manifest some abnormality of carbohydrate metabolism. Because the proportion of the American population older than 65 years is projected to increase from the current level of 12% to 22% by the year 2040, the burden of type 2 diabetes will become increasingly prevalent in the near future. As such, the dilemma of how best to care for these patients must be considered. Previous retrospective reports have suggested that long-acting sulfonylureas (such as chlorpropamide and glyburide) are more likely to cause hypoglycemia and should be avoided in elderly patients, but there are insufficient prospective, controlled data to support these claims. Although alternatives to sulfonylurea therapy have recently become available, these agents have the drawbacks of potential adverse gastrointestinal effects (eg, metformin, acarbose) and high cost (eg, metformin, troglitazone, acarbose). Thus, although hypoglycemia remains an appropriate concern for the elderly diabetic patients who use them, sulfonylureas are likely to remain a cornerstone of type 2 diabetes therapy.

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Values to milligrams per deciliter, divide by 0.05551.

Mean values; error bars, SE. To convert glucose to milligrams per deciliter, divide by 0.05551.

Healthy elderly patients with type 2 diabetes who receive maximal doses of a once-daily second-generation sulfonylurea agent during a short-term fast. Thus, although fasting is likely to remain a factor in the pathogenesis of hypoglycemia in a small percentage of patients with type 2 diabetes treated with sulfonylureas, this risk is not sufficient to withhold the use of these agents in otherwise healthy elderly patients. These results are contrary to the conclusions of numerous retrospective uncontrolled studies on the subject of sulfonylurea-induced hypoglycemia, which have identified age and energy restriction as the primary factors associated with hypoglycemia among type 2 diabetic patients. Other known associations with sulfonylurea-induced hypoglycemia include polypharmacy, alcohol abuse, and liver or kidney dysfunction. These data further suggest that healthy elderly sulfonylurea-receiving patients with type 2 diabetes are protected against the development of hypoglycemia during a short-term fast. Enhanced counterregulatory hormone secretion is a potential mechanism to explain this finding. Much published data are available describing the physiological response to hypoglycemia in type 1 diabetes, but the data are inconclusive with respect to type 2 diabetes. Because most patients with type 1 diabetes lose their ability to secrete glucagon in response to hypoglycemia shortly after developing diabetes, incremental secretion of epinephrine assumes a primary role in the hormonal response to hypoglycemia in this disease. Because the ability to secrete epinephrine is also impaired in approximately 25% of patients with long-standing type 1 diabetes mellitus, such patients may manifest the syndrome of “hypoglycemic unawareness,” resulting in a tendency to develop frequent, severe, and prolonged hypoglycemia. Healthy nondiabetic subjects begin to exhibit increments in epinephrine secretion at plasma glucose levels between 2.27 and 3.77 mmol/L (41 and 68 mg/dL) The fact that the subjects with type 2 diabetes in our study secreted epinephrine during hyperglycemia suggests that glucoregulatory centers in the hypothalamus are sensing neuroglycopenia and are responding by stimulating epinephrine secretion prior to the onset of global cortical dysfunction. This is consistent with observations in type 1 diabetes, where patients with poor glycemic control have been demonstrated to exhibit elevated glycemic thresholds for the development of hypoglycemic symptoms compared with nondiabetic subjects. The inability to demonstrate a clear glycemic threshold for epinephrine release during the placebo arm of the current study probably reflects the fact that plasma glucose concentration...
centrations did not drop below this threshold (about 8.9 mmol/L [160 mg/dL]) in most patients during the placebo study. In sum, our results suggest that enhanced incremental secretion of epinephrine protects against the development of cerebral neuroglycopenia in type 2 diabetes and may effectively preclude clinical hypoglycemia.

Interpretation of this study is limited by the fact that many of the participants exhibited suboptimal diabetes control, and as a result, these findings may not be applicable to patients with type 2 diabetes who achieve near-normal glycemic control. Many patients with type 2 diabetes do not achieve near-normal glycemia, however, and the glycosylated hemoglobin levels obtained at study entry are typical of patients with type 2 diabetes encountered in clinical practice. Moreover, when the subjects are analyzed by quartile according to fasting plasma glucose concentrations, it is evident that subjects in the lowest quartile had normal glycemia during the high-dose study (mean [SD] fasting glucose, 5.8 [0.8] mmol/L [104 (14) mg/dL]; mean (SD) nadir glucose, 3.9 [0.6] mmol/L [71 (11) mg/dL]; n=13), and these subjects did not develop hypoglycemia. Although the observed epinephrine increase may, theoretically, be attributable to factors other than the decline in plasma glucose, the fact that baseline epinephrine levels did not differ between the placebo and sulfonylurea studies suggests that the decline in plasma glucose was the primary stimulus for incremental epinephrine secretion. Concentrations of growth hormone and cortisol were not determined in this study, but these hormones have been shown not to be involved in the acute response to hypoglycemia. Finally, all of the subjects were receiving stable sulfonylurea treatment prior to study enrollment, so these results do not directly pertain to the risk of hypoglycemia among patients with type 2 diabetes with diet failure who fast shortly after initiating sulfonylurea therapy. Similarly, the rate of occurrence of hypoglycemia may be higher in actual clinical practice than was observed in this carefully controlled clinical trial.

One unresolved issue regards the pathogenesis of severe sulfonylurea-induced hypoglycemia, which, although uncommon, does occur in clinical practice. Although many of the reported cases of sulfonylurea-induced hypoglycemia are attributable to intentional overdose or otherwise inappropriate sul-
fonylurea ingestion, the mechanism of life-threatening hypoglycemia in appropriately treated patients with type 2 diabetes remains to be elucidated. It may be that other causes of hypoglycemia, such as ethanol ingestion or strenuous exercise, play a significant role in these cases, although a recent report suggests that moderate exercise is well tolerated among fasted, sulfonylurea-receiving patients with type 2 diabetes. Other known factors, such as the presence of underlying renal disease, hepatic dysfunction, or intercurrent illness, are also likely to be important in the pathogenesis of hypoglycemia secondary to sulfonylureas. Alternatively, it is possible that type 2 diabetes is analogous to type 1 diabetes in that those patients who are unable to secrete epinephrine in response to a hypoglycemic stimulus are at an increased risk for the development of severe hypoglycemia. If this is the case, then prospective identification of these patients may be useful in determining appropriate treatment goals for these patients.

In summary, our study emphasizes that hypoglycemia is rare among healthy, sulfonylurea-receiving, elderly patients with type 2 diabetes during a short-term fast. Moreover, these data suggest that incremental secretion of epinephrine at elevated glucose thresholds may play a pivotal role in the prevention of sulfonylurea-induced hypoglycemia. From a clinical standpoint, the second-generation oral sulfonylurea agents should be considered safe for use in elderly, fasted patients with type 2 diabetes provided that the presence of other hypoglycemia risk factors, such as alcohol, are excluded.

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