

Severe Hypoglycemia Monitoring and Risk Management Procedures in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial

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Hypoglycemia is a potentially serious side effect of blood glucose lowering in diabetes mellitus. The intensive glycemia treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is designed to treat patients with type 2 diabetes with target glycemia within the normal range (ie, glycosylated hemoglobin <6%). Because it is known that treating glycemia to such a low level in patients with diabetes will result in episodes of hypoglycemia, it is necessary to address prevention and treatment of such episodes to ensure patient safety. Thus, several approaches are being taken in the ACCORD trial to prevent initial episodes of severe hypoglycemia, to monitor the frequency of episodes that do occur, and to prevent recurrence. This report describes the processes used in the ACCORD trial, including the definition of severe hypoglycemia, the type of education provided to participants and staff members to prevent initial and subsequent episodes of severe hypoglycemia, and the monitoring systems implemented to identify severe hypoglycemia and prevent its recurrence. The ACCORD trial conducts review and oversight of individual cases of severe hypoglycemia and monitors rates of severe hypoglycemia by clinical site and treatment arm. If the ACCORD intensive glycemia treatment is found to be efficacious in preventing cardiovascular disease events, assessment of the risk and benefit will be essential. In addition, translation of the principles behind the monitoring of severe hypoglycemia in ACCORD into feasible strategies for use in clinical practice will be needed. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99[suppl]:80i–89i)

Hypoglycemic events occur commonly in patients with both type 1 and type 2 diabetes mellitus.^{1,2} Indeed, hypoglycemia is so common that it is considered an unavoidable conse-

quence of the management of diabetes. However, hypoglycemia, because of its significant effects on a patient's activities of daily living and social relationships as well as risk

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for serious injury, is often the limiting factor in achieving physiologic glucose levels with diabetes therapy.^{3,4}

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is a multicenter, randomized controlled trial involving 10,251 patients with type 2 diabetes and nonoptimal levels of blood pressure or blood lipids who are at high risk for having a cardiovascular event. A primary specific aim of the ACCORD trial is to determine the effect of a therapeutic strategy (intensive) that targets a glycosylated hemoglobin (HbA_{1c}) level of <6.0% compared with a strategy (standard) that targets an HbA_{1c} level of 7.0%–7.9% (expected median level, 7.5%) on the rate of major cardiovascular events. Details regarding the design of the trial and the glycemia intervention strategies are presented elsewhere in this supplement.^{5,6}

Because ACCORD is targeting physiologic blood glucose levels in the intensive group, episodes of severe hypoglycemia are expected. Moreover, as a result of the lower targeted levels, severe hypoglycemic episodes are expected more frequently in the intensive glycemia treatment group than in the standard glycemia treatment group. Although severe hypoglycemia is expected, attention still must be paid to monitoring the safety of participants and making treatment changes as necessary to ensure their safety. Thus, the close monitoring of participants for severe hypoglycemia is an important aspect of safety monitoring in ACCORD.

The first participants were recruited into the vanguard phase of the ACCORD trial ($n = 1,174$), which was the feasibility phase for the main trial.⁵ Patients were recruited and randomized for 4.5 months (January 11, 2001, through June 1, 2001) and then treated and followed for 1 year. The main trial protocol was modified on the basis of what was learned during the vanguard phase, including strategies for identifying, monitoring, and reducing severe hypoglycemic events. Investigator and staff member training was developed for the vanguard phase and modified for the main trial. The investigators and staff members were trained to deliver patient education, and patient education materials were provided by the study. This report describes participant and staff member educational approaches, as well as the monitoring strategy and processes used in the ACCORD trial.

Although the treatment approaches are experimental and not designed for current delivery in clinical practice, the principles underlying the attention to severe hypoglycemic events as a consequence of intensive glycemia lowering will be relevant to clinical practice if the ACCORD trial determines that intensive glycemia lowering does in fact reduce cardiovascular disease (CVD) events in patients with type 2 diabetes at high risk for CVD.

Action to Control Cardiovascular Risk in Diabetes Study Structure

The ACCORD trial comprises the Coordinating Center and 7 clinical center networks (CCNs), each of which has multiple

clinical sites, which are contracted by the National Heart, Lung, and Blood Institute (NHLBI). These groups work together through the Steering Committee, subcommittees, and working groups to successfully design and conduct the trial. Each CCN has a principal investigator and coordinator, as does each clinical site. The CCNs provide investigators and staff members to serve on various studywide committees and working groups.⁵ ACCORD uses a distributed Web-based data system for data entry by the 77 clinical sites. This system enables rapid feedback and data analysis for use in monitoring by the various committees and working groups.

The responsibilities of the Glycemia Working Group include the glycemia treatment approach and the review of severe hypoglycemia cases. The Internal Hypoglycemia Monitoring Committee, composed of study investigators and NHLBI staff members, provides additional internal oversight for monitoring severe hypoglycemia. External oversight groups are appointed by the NHLBI and include the Data and Safety Monitoring Board (DSMB) and the External Hypoglycemia Monitoring Committee.

The role of each of these groups and the use of the Web-based data entry system in the processes for monitoring severe hypoglycemia in ACCORD are described later.

Severe Hypoglycemia Monitoring and Rates in Other Large Studies of Diabetes

Several large clinical trials of diabetes treatment have monitored the rates of severe hypoglycemia in their participants.^{7–12} Table 1 lists the definitions of severe hypoglycemia used in each of the major studies. Each trial that formally defined severe hypoglycemia used the necessity for assistance by another person in treatment of the episode as the key portion of its definition. Additional factors considered in the definitions included prompt recovery with appropriate therapy or the documentation of low blood glucose.^{7,11}

Rates of severe hypoglycemia in trials of type 2 diabetes have been low, 1.4% of participants per year in the United Kingdom Prospective Diabetes Study (UKPDS) study⁹ in the intensively treated group receiving insulin, albeit with attained median HbA_{1c} levels in the 7.0%–7.4% range. In the DCCT, a trial of 1,441 patients with type 1 diabetes, there were 62 episodes of hypoglycemia requiring assistance per 100 patient-years in the intensively treated group (median HbA_{1c}, 7.2%) compared with 19 episodes per 100 patient-years in the conventional treatment group (median HbA_{1c}, 9.1%).⁷

The best estimate of the risk for severe hypoglycemia in a general population was obtained between June 1997 and May 1998 in a Scottish community of 367,051 using a validated diabetes registry and linkage with emergency services.¹³ Severe hypoglycemia in that study was defined as an episode requiring emergency assistance from healthcare professionals, along with a blood glucose level <3.5 mmol/L (63 mg/dL). Overall, 1.2% of all patients with type

Table 1
Severe hypoglycemia definitions used in major glycemia trials

Trial	Definition	HbA _{1c} in Intensive Group
Type 2 diabetes mellitus		
UKPDS ⁹	Requiring help from another person	7.1%
Kumamoto Study ¹⁰	Requiring help from another person	7.1%
DIGAMI ¹²	Not defined	7.0%
VA CSDM ¹¹	Requiring help from another person and either a prompt recovery with therapy or a confirmed low glucose level (not defined)	<7.3%
Type 1 diabetes		
DCCT ⁷	Requiring the assistance of another person and either a blood glucose level <50 mg/dL (2.8 mmol/L) or prompt recovery with oral carbohydrate, glucagon, or intravenous glucose	7.0%
ACCORD	Requiring medical or paramedical attention in which there was either a documented capillary glucose level <50 mg/dL (2.8 mmol/L) or in which prompt recovery was achieved with oral carbohydrate, intravenous glucose, or glucagons	<6.0%

ACCORD = Action to Control Cardiovascular Risk in Diabetes trial; DCCT = Diabetes Control and Complications Trial; DIGAMI = Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction trial; HbA_{1c} = glycosylated hemoglobin; UKPDS = United Kingdom Prospective Diabetes Study.

2 diabetes and 7.3% of all patients with diabetes who were using insulin had ≥ 1 episodes during a 1-year period; risk factors were older age, longer duration of diabetes, and lower HbA_{1c}.¹³

Definition of Severe Hypoglycemia in Action to Control Cardiovascular Risk in Diabetes

The definition of severe hypoglycemia in ACCORD is similar to definitions used in other trials. Mild hypoglycemia is defined as self-reported transient symptoms, such as light-headedness, tremor, shaking, sweating, tingling, blurry vision, trouble concentrating, and so on, that resolve after self-treatment with the ingestion of simple carbohydrates. Severe hypoglycemia is defined as hypoglycemia with documented blood glucose <2.8 mmol/L (50 mg/dL) or symptoms that promptly resolve with oral carbohydrate, intravenous glucose, or glucagon that require the assistance of medical or paramedical personnel. In ACCORD, these events are subject to special monitoring.

Educational Strategies to Reduce Severe Hypoglycemic Events

Provider and staff member training: Diabetes experts at an initial meeting provided training for all ACCORD investigators and staff members. The training addressed glycemia treatment and monitoring, data recording, assessing participants, and revising treatments on the basis of those assessments. Suggested algorithms guiding glycemic therapy for standard and intensive groups were reviewed, and available glycemia medications were described, including dosing and potential side effects. Insulin therapy was discussed, including a thorough review of various types of insulin and multidosing options. Providers and staff members were trained to teach ACCORD participants to self-monitor their blood glucose levels at frequencies based on assigned treatment group (standard

or intensive) and whether they were receiving insulin or oral medication therapies. Target ranges for HbA_{1c}, before-meal blood glucose, 2-hour postprandial blood glucose, and bedtime blood glucose levels were reviewed. Aspects of participants' lifestyles, including physical activity levels, stress and support systems, medications, and food choices, that influence blood glucose levels were emphasized as important for safe glycemic control. Strategies to help participants reduce the risk for severe hypoglycemia, such as delaying insulin until arrival at the restaurant when going out to eat and having a carbohydrate snack before vigorous physical activity, were provided. ACCORD's severe hypoglycemia definitions, classifications, causes, symptoms, and treatments were reviewed. The physiologic events related to severe hypoglycemic symptomatology were discussed, emphasizing an individualized approach. Specific case examples were provided and discussed.

This initial training has been followed by refresher courses every 1–2 years, at which staff members and investigators, including those new to the ACCORD trial, receive case-based training in the safe lowering of blood glucose levels and share strategies and approaches with one another. These subsequent training sessions review many of the concepts from the original training sessions, including approaches to achieving glycemic targets safely, determining risk factors for the development of severe hypoglycemia, educating participants in techniques to avoid severe hypoglycemia, and the appropriate treatment for and documentation of hypoglycemic episodes. For the postvanguard trial, specific sessions are held on severe hypoglycemia recognition, prevention, and treatment, with a particular focus on the prevention of recurrence.

In addition to these in-person meetings, tips are provided on the study's Web site as well as in electronic weekly study updates, education sheets are available on the ACCORD Web site, and diabetologists and diabetes educators are available for consultation.

Patient education: The goals of the study are reviewed with each participant during the informed consent process.

Each participant receives education about the disease process, potential adverse events, and glycemia monitoring, as well as how to recognize and treat severe hypoglycemia. ACCORD uses an individualized approach based on suggested algorithms and the teaching and reinforcement of appropriate finger-stick self-monitoring blood glucose technique and frequency. Intensive-group participants who are not taking insulin are requested to perform self-monitored blood glucose checks. If a participant is taking insulin in the intensive group, he or she is requested to perform additional monitoring. Standard-therapy participants not taking insulin are requested to conduct self-monitored blood glucose checks at less frequent intervals. Participants are taught to record their glucose levels in a logbook and to bring logs to clinic visits for collaborative review by both the participants and their providers. Home finger-stick self-monitoring blood glucose devices can be brought in to clinics, and results are reviewed by study staff members or downloaded into a laptop computer for further evaluation, such as patterns of low glucose measurements.

All participants are taught how to recognize and self-treat hypoglycemia, including keeping glucose tablets (provided by the study) available at all times. Participants are taught to manage minor hypoglycemia by eating or drinking carbohydrates. In addition to the treatment of mild hypoglycemia, prevention through lifestyle modification is emphasized. Participants are taught to test their blood glucose before and after exercise and to inform study staff members if they start weight loss programs so that medication adjustments can be made. The effect of changes in food intake frequency or amount on blood glucose levels is reviewed, and participants are asked about dietary changes. Physical activity is encouraged, and its effects on blood glucose levels and hypoglycemia are reviewed. Other factors, such as illness, shift work, and vacations, are discussed as needed, and strategies are developed to avoid hypoglycemia. Patient educational materials for hypoglycemia are provided in the form of wallet cards, cartoons, and pamphlets, and this content is reinforced on a regular basis.

At each visit, participants are asked if they have experienced any hypoglycemic episodes. All episodes of severe hypoglycemia are reviewed by the provider, and adjustments to medication or lifestyle recommendations are made if necessary. Those who have experienced episodes of severe hypoglycemia are provided glucagon kits, along with instructions about how to administer them, which are given to participants and anyone living with them.

Monitoring Severe Hypoglycemia in Action to Control Cardiovascular Risk in Diabetes

Monitoring hypoglycemia in ACCORD occurs at 2 levels: individual cases and groups of participants. Individual cases are reviewed by the clinical site principal investigator and study coordinator and monitored centrally through a strin-

gent review and feedback process, with the goal of preventing repeat episodes in these participants. The monitoring of groups includes rates of severe hypoglycemia by the clinic site and CCN to identify potential outlier sites with high rates of severe hypoglycemia and assist them in identifying areas for improvement. DSMB monitoring also includes the review of rates of severe hypoglycemia by randomized treatment group to determine whether the strategies used to lower glycemia are placing participants at excessive risk.

Individual case monitoring: Because of the potential risk to individual participants, ACCORD investigators and staff members carefully review each case of severe hypoglycemia (see Figure 1). The goal of this review is to identify and correct any underlying causes of the hypoglycemic event to prevent future events in that participant.

This review starts with documentation for all severe hypoglycemic events, which is completed by clinical sites on the Severe Hypoglycemia Action Form. Information about an event is recorded, which includes symptoms; insulin doses immediately before the event; finger-stick blood glucose levels before the event; antecedents such as changes in medication, illness, or diet; consequences such as hospitalizations or injuries; and actions taken by the clinic site, such as changing medication, additional self-monitoring blood glucose testing, and/or additional participant education.

Severe hypoglycemic events that require medical attention undergo additional review. These events are considered serious adverse events and require the completion of appropriate study forms and reporting to local institutional review boards and the DSMB. Additionally, these events undergo stringent review by study personnel and by an external monitoring group. If an event is the first for a participant, the Glycemia Working Group representative (a diabetologist) for that clinical site reviews the data entered on the Severe Hypoglycemia Action Form to evaluate whether the data entered and response to the event were appropriate or whether additional data or review are needed. If the representative believes that additional review or clarification is needed, he or she contacts the site for a discussion of the case. Once the Glycemia Working Group representative has determined that management was appropriate, the event is reviewed by the safety officer at the ACCORD Coordinating Center, and the review is complete.

If a participant has a second hypoglycemic event requiring medical assistance, additional scrutiny occurs. Clinical sites complete study forms as described previously. However, before the Glycemia Working Group representative reviews the case, the clinical site principal investigator is required to provide additional information, including a narrative providing details on the underlying cause of the event and actions taken to prevent further episodes. Upon completion of the narrative, the Glycemia Working Group representative then reviews all documentation on the case,

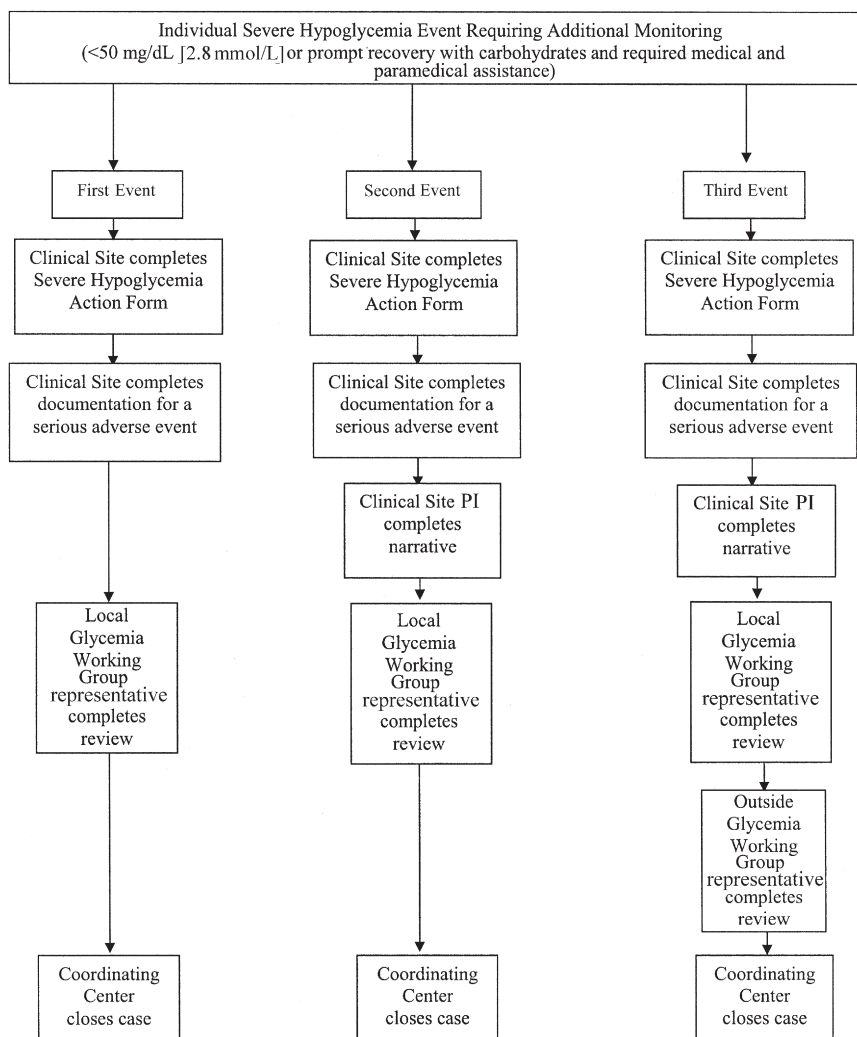


Figure 1. Steps for the review of individual severe hypoglycemic events. PI = principal investigator.

contacts the clinical site principal investigator to discuss the case and provide feedback on management, and completes his or her own narrative describing the findings. Upon completion of these steps, the Coordinating Center safety officer reviews all documentation, and the review is complete.

If a participant has ≥ 3 of these events, 2 additional steps occur before the review is complete. First, the documentation is reviewed for appropriateness of the response by a Glycemia Working Group representative who is not part of the CCN of the clinical site, who prepares a brief narrative report and action plan. Second, to minimize the possibility of even more events, the clinical site principal investigator must set a new, higher HbA_{1c} goal for the participant and adjust the participant's medication as needed to meet this new goal. For example, instead of an intensive-group participant having an HbA_{1c} goal of <6%, the goal may be relaxed to <6.5% or <7.0%. Upon completion of these steps, the Coordinating Center safety officer reviews all documentation and the new HbA_{1c} goal, and the review is complete. If a participant continues to have additional

events after the relaxation of the goal, the Glycemic Working Group representative works with the clinical site staff members and investigators to determine the particular barriers for that participant and create a treatment plan that will minimize the chance of future episodes of severe hypoglycemia.

Monitoring group-level rates of severe hypoglycemia: In addition to monitoring individual cases, as described previously, rates of severe hypoglycemia are scrutinized according to CCN, clinic site, and treatment arm. Three monitoring groups review the rate of severe hypoglycemia to ensure that participants' safety is maximized (Figure 2).

INTERNAL HYPOGLYCEMIA MONITORING COMMITTEE. The Internal Hypoglycemia Monitoring Committee was established to monitor rates of severe hypoglycemia overall and by study site and to ensure that all study sites are maximizing efforts to lower the rate of severe hypoglycemia. This committee was established to ensure internal study oversight of severe hypoglycemia as a side effect of

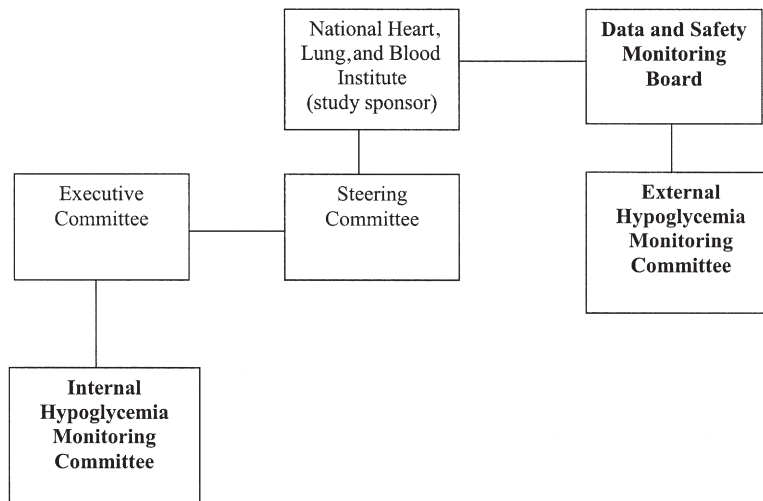


Figure 2. Reporting structure for Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial severe hypoglycemia monitoring groups. Monitoring groups are shown in bold type.

the intensive glucose lowering. The committee consists of members from the NHLBI Project Office, the Executive Committee, the Coordinating Center, and representatives from the Steering Committee. It is chaired by a diabetologist. None of the members see patients within the ACCORD trial.

Rates of severe hypoglycemia across the study are examined at regular intervals. Changes in rates over time are reviewed to ensure that the education and monitoring processes are effective. Subgroup analysis and regression methods are used to identify predictors of severe hypoglycemia, including initial and multiple events. These results are conveyed to investigators so they can be alert to participants at high risk. This committee also may identify additional materials or processes needed by the study and oversee their development.

This committee also monitors clinic-specific severe hypoglycemia rates. Every 6 months, a report of clinical sites with ≥ 1 severe hypoglycemic event is prepared, including the previous 18-month incidence rate of events and the absolute number of events in the previous 6 months. The 18-month period was chosen to allow sufficient time for the calculation of a meaningful incidence rate and to allow clinics that had 1 period of multiple events but no subsequent events to eventually move off the list. Clinics are ranked by severe hypoglycemia rate; CCN principal investigators and coordinators are notified if any clinics in their clinical center networks have rates in or near the top 10% during the monitoring period, and the principal investigators and coordinators are requested to work with those clinics to lower the rates.

If a clinic is in the top 10% for 2 consecutive monitoring periods, additional action occurs. The Internal Hypoglycemia Monitoring Committee requests from the CCN principal investigator and coordinator a letter written in conjunction with the clinical site principal investigator and coordinator explaining the continued high rate and describ-

ing steps they are taking to minimize future severe hypoglycemic episodes. Potential steps may include the additional training and education of clinic staff members, changes to clinic procedures, the review and revision of the content of study visits, modification of the use of particular medication, and/or change in the technique used to communicate with participants. The response is reviewed by members of a joint subcommittee of the Internal Hypoglycemia Monitoring Committee and Glycemia Working Group, including diabetologists, as well as Coordinating Center investigators and staff members and diabetes educators. If a clinic remains in the top 10% for ≥ 3 consecutive monitoring periods, further action may be taken to assist the clinic, such as a conference call with the CCN principal investigator and coordinator, clinic principal investigator and coordinator, and representatives from the subcommittee or a site visit by members of the subcommittee.

EXTERNAL HYPOGLYCEMIA MONITORING COMMITTEE. The ACCORD External Hypoglycemia Monitoring Committee is an advisory committee to the ACCORD DSMB and as such reports to the DSMB and to the NHLBI. It was established to assist the DSMB with monitoring severe hypoglycemia, in response to a recommendation by the DSMB, and is composed of experts in the field of diabetes management. The External Hypoglycemia Monitoring Committee reviews study procedures for identifying, responding to, and monitoring severe hypoglycemic events; monitors rates and sequelae of severe hypoglycemic events in the trial; makes recommendations to the ACCORD DSMB and NHLBI regarding the adequacy of study procedures for preventing and treating severe hypoglycemia; and comments on the magnitude of the observed rates in the context of community studies and other clinical trials. The committee does not review rates of severe hypoglycemic events by treatment group. The committee may recommend the collection of additional information, the establishment

of additional processes within the study to minimize severe hypoglycemic risk, or review by the DSMB of specific issues.

DSMB. The DSMB generally meets twice a year to review study progress as well as safety data, including data on severe hypoglycemia. The DSMB reviews individual cases of severe hypoglycemia, focusing on participants with multiple events, and rates of severe hypoglycemia, including rates by treatment group, as well as recommendations of the External Hypoglycemia Monitoring Committee. The board may suggest additional education or levels of monitoring to ensure the safety of ACCORD participants.

Conclusion

Monitoring severe hypoglycemia is a major component of the safety monitoring in the ACCORD trial. Although other diabetes treatment trials have tracked severe hypoglycemic events, ACCORD has established a rigorous review and monitoring process designed to reduce events. There is careful scrutiny of individual cases by study personnel and external monitoring groups. Additionally, the rate of severe hypoglycemic events by clinic site, treatment group, and demographic characteristics is carefully monitored, and corrective steps are taken to minimize the overall risk to all participants in the trial. This significant infrastructure is substantially greater than in any other trial of diabetes treatment but was believed to be necessary to maximize participants' safety while achieving the very low target of HbA_{1c} in the intensive treatment group.

Whether or not intensive glycemia lowering tested in a randomized, prospective trial does in fact reduce future CVD events in patients with diabetes is still unknown. However, if the ACCORD trial confirms that hypothesis, then attention in clinical practice to the potential consequences of intensive treatment, particularly for severe hypoglycemia, will be necessary. The strategies used for monitoring and reducing severe hypoglycemia in the ACCORD trial are undoubtedly greater than could be used in routine clinical practice. If the ACCORD intensive glycemia treatment intervention proves to be efficacious in preventing cardiovascular events, translation of the ACCORD approach to hypoglycemia into feasible strategies for use in clinical practice will be needed.

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Appendix

The Action to Control Cardiovascular Risk in Diabetes

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