Evolution of the Lipid Trial Protocol of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial

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The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial aims to test whether a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) plus a fibrate is more efficacious in reducing cardiovascular events than a statin plus placebo in patients with type 2 diabetes mellitus with defined glycemic control. This is a blinded component in a 5,518-patient subset of the ACCORD cohort. These participants were randomized to either be (1) treated with simvastatin (titrated to 40 mg/day if necessary to achieve a goal low-density lipoprotein [LDL] cholesterol level of <2.59 mmol/L [100 mg/dL]) plus placebo or (2) treated to the same goal LDL cholesterol level with the statin plus active fenofibrate 160 mg/day or its bioequivalent (or 54 mg/day if the estimated glomerular filtration rate ranges from 30 to <50 mL/min per 1.73 m^2). Setting an upper limit of LDL cholesterol qualifying for randomization excluded patients who would not likely achieve the LDL cholesterol goal. Recruitment for ACCORD began in January 2001, and follow-up is scheduled to end in June 2009. Since recruitment began, several clinical trials and consensus statements have been published that led to changes in the details of the lipid treatment algorithm and protocol. This report describes the design of the lipid protocol and modifications to the protocol during the course of the study in response to and in anticipation of these developments. The current protocol is designed to provide an ethically justifiable test of combined statin plus fibrate treatment consistent with the highest level of safety and lipid treatment standards of care. **(Am J Cardiol 2007;99[suppl]:56i–67i)**

The reduction of cardiovascular risk is the most important goal in the pharmacologic management of dyslipidemia in high-risk populations. Because event rates remain higher in patients with diabetes mellitus than in those without diabetes despite increasingly intensive care, 2 new strategies have been discussed: the reduction of low-density lipoprotein (LDL) cholesterol to a lower concentration than advocated in the current guidelines and the treatment of high-density lipoprotein (HDL) cholesterol and triglycerides in addition to LDL cholesterol. The former strategy has been and is being tested in several clinical trials, but the latter has not previously been tested. For this reason, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial investigators developed a protocol for the lipid component of the overall ACCORD trial to answer the following question: In the context of good glycemic control, does a therapeutic strategy that uses a fibrate to increase HDL

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cholesterol and lower triglyceride levels together with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) to lower LDL cholesterol reduce the rate of cardiovascular disease (CVD) events compared with a strategy that uses a statin plus a placebo?

This report presents the rationale, initial ACCORD lipid trial design, and modifications to the design of the lipid protocol during the first 3.5 years of the trial in response to new knowledge and changes in guidelines for lipid management.

Background: Overall Action to Control Cardiovascular Risk in Diabetes Design and the Lipid Trial Component

Details regarding the overall rationale and design of ACCORD in general can be found elsewhere in this supplement.[1,2] Briefly, the overall goal of the ACCORD trial is to test 3 complementary medical treatment strategies for reducing the rate of major CVD morbidity and mortality in type 2 diabetes mellitus. It was designed as a randomized, multicenter, double 2 × 2 factorial trial in 10,000 patients with type 2 diabetes. Ultimately, 10,251 participants were recruited. The trial is designed to test the effects on preventing major CVD events of intensive glycemic control, treatment to increase HDL cholesterol and lower triglycerides (in the context of good LDL cholesterol and glycemic control), and intensive blood pressure control (in the context of good glycemic control). All 10,251 participants are in the glycemia trial. In addition, one 2 × 2 trial will address the blood pressure question in 4,733 of the recruited participants, while the other 2 × 2 trial will address the lipid question in 5,518 of the participants. Therefore, each participant will be in a 2 × 2 trial testing 2 treatment strategies of 2 interventions, one of which is always glycemic control and the other is either lipid or blood pressure control. The lipid component is the only masked portion of the trial.

The primary outcome measure for each part of ACCORD is the first occurrence of a major CVD event, specifically nonfatal myocardial infarction (MI) or stroke or cardiovascular death. Participants were recruited over 2 noncontiguous periods (the vanguard phase and the main trial), and follow-up is planned for about 4–8 years (approximate mean, 5.6 years).[2]

Rationale for the Action to Control Cardiovascular Risk in Diabetes Lipid Hypothesis

The design of ACCORD began in 1999. The guidelines for the management of dyslipidemia at the time were the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) II.[3] These 1993 guidelines considered LDL cholesterol as the cornerstone of lipid management, but by 1999, they were outdated. In particular, the ATP II guidelines were formulated before the publication of results of the major statin trials, and they identified bile acid–binding resins as the drugs of first choice for the management of elevated LDL cholesterol. In addition, ATP II stratified risk (for people free of CVD) on the basis of adding together the number of risk factors a person possessed rather than identifying people with multiple risk factors and then stratifying risk factors according to their severity (as the 2001 update of these guidelines, ATP III, recommended).[4] In ATP II, diabetes was one of the important risk factors (along with smoking, hypertension, age, sex, and HDL cholesterol) but was not considered as important a risk factor for CVD as prevalent vascular disease per se (coronary, cerebral, or peripheral vascular disease). ATP II defined the treatment initiation level and target level of LDL cholesterol for patients with vascular disease as 3.36 mmol/L (130 mg/dL) and ≤2.59 mmol/L (≤100 mg/dL), respectively. There was a "gray zone" for LDL cholesterol of 2.59–3.36 mmol/L (100–130 mg/dL), for which management was left up to clinicians. During the ACCORD planning phase, it was known that a revision of the guidelines was under way and that, most importantly, statins were the first-line agents for the management of elevated LDL cholesterol, as a result of the Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) trial, the Long-Term Intervention With Pravastatin in Ischaemic Disease (LIPID) trial, the West of Scotland Coronary Prevention Study (WOSCOPS), and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)—landmark clinical trials that established their efficacy for the reduction of cardiovascular events and their safety and tolerability.[5–9] New data from the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) study also supported the use of fibrates for the reduction of coronary artery disease (CAD) events and stroke[10] and confirmed previous results of the Helsinki Heart Study (HHS).[11] In addition, it was anticipated that the ATP III guidelines would suggest lower thresholds for the treatment of LDL and would consider diabetes as a CAD "risk equivalent."

Several concerns remained, however, even with implementation of the ATP III guidelines for the management of dyslipidemia in high-risk populations. For example, cardiac event rates in the actively treated groups of 4S, CARE, and LIPID remained at a very high level of ≥20% every 10 years, even in populations with effective statin treatment to a mean LDL cholesterol level of about 2.59 mmol/L (100 mg/dL). This was particularly evident in the subsets of effectively treated patients with diabetes in these trials, in whom event rates ranged from 31%–58% every 10 years. Similarly, despite marked reductions in events with fibrate management, cardiac event rates remained high in the active treatment group of the insulin-resistant subset of VA-HIT.[12]

Thus, during the development of the ACCORD lipid protocol, 2 strategies were considered that might further reduce these high event rates in a high-risk population: (1) the further reduction of LDL cholesterol beyond the

ATP III target of <2.59 mmol/L (100 mg/dL) and (2) combination treatment using a statin and a second agent (niacin or a fibrate) that would lower serum concentrations of triglyceride and increase HDL cholesterol. Because it was known in 1999 that the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT), the Treating to New Targets (TNT) trial, the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), and the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial would provide answers to the question of the efficacy and safety of a targeted LDL cholesterol level <2.59 mmol/L (100 mg/dL),[13–16] the ACCORD investigators thought that it was more important to test combination therapy than intensive LDL cholesterol lowering beyond the level specified by the guideline then in force (<2.59 mmol/L [100 mg/dL]).

The question of the relative efficacy of combination therapy was compelling for 2 reasons: (1) the relative risk versus benefit of combination therapy was not defined in a population with diabetes that characteristically presented with high triglycerides and low HDL cholesterol but in whom LDL cholesterol concentrations were typically either no different or mildly elevated compared with patients without diabetes and (2) only the Lipids in Diabetes Study (LDS)[17] was known to have initiated a test of combined therapy for the reduction of cardiovascular events. The LDS was designed and initiated as a 2 × 2 factorial trial of fenofibrate and cerivastatin over 5 years in 5,000 patients with type 2 diabetes but was stopped early because of concerns about the toxicity of cerivastatin.

A fibrate rather than niacin was selected as the drug to be tested in ACCORD, because VA-HIT and HHS had shown benefits of fibrate in populations with overrepresentation of diabetes and the metabolic syndrome. Also, there was concern that even the small reductions in insulin sensitivity accompanying niacin therapy[18] would make it more difficult to achieve intensive glycemic control in the overall glycemic trial. It was also necessary to address the safety of fibrate use in the setting of statin treatment, because the potential for increased myopathy with combination therapy (particularly the combination of statin with gemfibrozil) was well recognized. Ultimately, fenofibrate and simvastatin were chosen as the fibrate and statin for the trial. The choice of fenofibrate rather than gemfibrozil as the study medication proved fortuitous insofar as it has been subsequently demonstrated that a significant pharmacodynamic interaction exists between gemfibrozil (but not fenofibrate) and simvastatin (see the following discussion).

Evolution of the Action to Control Cardiovascular Risk in Diabetes Lipid Protocol

As noted previously, recruitment and follow-up for ACCORD was divided into a vanguard phase (January 2001 to December 2002) and a main trial phase (February 2003 to June 2009). The vanguard phase evaluated recruitment and treatment strategies for all components of the trial, including the lipid component, before the institution of the full trial. Lessons learned from the vanguard phase were incorporated into the main trial protocol. Protocol changes in lipid trial eligibility and treatment made from the initiation of the trial through the present are listed in Table 1.

Vanguard phase protocols (January 2001 to December 2002): To test the hypothesis that a fibrate plus a statin is more efficacious than a statin alone in reducing CVD events without compromising safety, it was decided at the beginning of the vanguard phase that all participants in the lipid component would be treated with unblinded simvastatin to a minimal LDL cholesterol goal of <3.36 mmol/L (130 mg/dL) but that the study would randomly assign participants to fenofibrate or its placebo in a blinded fashion. There were 2 important questions regarding the implementation of this design: (1) How could the study ensure that participants medicated with a variety of statins and doses of statins at baseline would achieve acceptably low LDL cholesterol levels with simvastatin? (2) How would the study ensure the safety of the combination therapy in light of the known potential side effects of the drugs in combination? In addition, the ACCORD investigators recognized the need to deal with the possibility that a small number of patients might become refractory to treatment and develop serum concentrations of LDL cholesterol and triglycerides greater than the levels the guidelines then recommended. This necessitated incorporating into the protocol an option for titration of the statin.

Although the ACCORD investigators understood that the ATP III guidelines would continue to recommend an LDL cholesterol treatment initiation level of >3.36 mmol/L (130 mg/dL) for high-risk patients, a lower threshold was chosen in ACCORD to enhance the cardiac protection of the statin, specifically >3.10 mmol/L (120 mg/dL). For the vanguard phase, the protocol called for a maximum dose of simvastatin of 20 mg/day for safety (see the following discussion) and developed a titration algorithm with doses of 0–20 mg/day for those patients with LDL cholesterol >3.10 mmol/L (120 mg/dL). Because patients with LDL cholesterol >4.40 mmol/L (170 mg/dL) would require doses of simvastatin >20 mg/day to achieve an LDL cholesterol level <2.59 mmol/L (100 mg/dL), they were not eligible for the ACCORD lipid component.[2] Because such high LDL cholesterol levels are uncommon in patients with diabetes, the ACCORD investigators anticipated that this criterion would not exclude many from the trial. With this approach, it was estimated that patients with up to the highest allowable baseline LDL cholesterol levels (4.40 mmol/L [170 mg/dL]) would achieve an LDL cholesterol level of approximately 2.84 mmol/L (110 mg/dL), assuming a 35% reduction in LDL cholesterol in those participants treated with simvastatin 20 mg/day. This titration algorithm attempted to

Table 1
Changes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid protocol over time*

Protocol Element	Vanguard Phase (January 2001–December 2002)		Main Trial (Went into Effect January 2003)		
	10/16/00 Protocol	9/13/01 Protocol	11/14/02 Protocol	8/31/04 Protocol	5/11/05 Protocol
LDL-C eligibility criterion	≤170 mg/dL	Same	85–170 mg/dL	60–180 mg/dL	Same
HDL-C eligibility criterion	<50 mg/dL	Same	Same	<55 mg/dL, women or African American; <50 mg/dL all others	Same
Starting dose of statin	0 if LDL-C <116 mg/dL 5 mg/day if LDL-C 116–150 mg/dL 10 mg/day if LDL-C 151–170 mg/dL	Same	All 20 mg/day No titration	All 20 mg/day to start except ppts with CVD = 40 mg/day	Same
LDL-C level for statin uptitration	Initial 120 mg/dL Subsequent 130 mg/dL	120 mg/dL for all	No titration	Uptitrate to 40 mg/day if LDL >100 mg/dL × 2	Same, with addition to uptitrate to 40 mg/day if ppt has CVD event
LDL-C alert: D/C study medications	If 130 mg/dL × 2 and on maximum statin dose, D/C blinded medications/transfer	Same	Same	If >120 mg/dL × 2 and on 40 mg/day statin, D/C blinded medications/transfer	Same
Triglyceride alert	If >750 mg/dL × 2, D/C blinded medications/transfer	Same	Same	Same	Same
Downtitrate statin	<50 mg/dL	Same	If <40 mg/dL × 2, D/C statin	Same	Same
Fibrate dose	160 mg/day	Same	Same	54 or 160 mg/day (or bioequivalent doses) based on GFR	Same

CVD = cardiovascular disease; D/C = discontinue; fibrate = fenofibrate; GFR = glomerular filtration rate estimated by the Modified Diet in Renal Disease equation (see text for details); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; ppt = participant; statin = simvastatin (a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor); transfer = transferring this aspect of patient care back to participant's private physician.

* For HDL-C and LDL-C, 1 mg/dL = 0.02586 mmol/L.

† For triglyceride, 1 mg/dL = 0.01129 mmol/L.

reach appropriate LDL cholesterol goals while using the lowest efficacious dose of simvastatin in combination with a fibrate.

The initial dose of simvastatin was tailored to the participant's observed (or estimated; see the following discussion) baseline LDL cholesterol level (Table 1). For participants whose LDL cholesterol was <2.97 mmol/L (115 mg/dL), no treatment was initiated. For those with LDL cholesterol of 3.00–3.88 mmol/L (116–150 mg/dL), simvastatin therapy was initiated at 5 mg/day. For those with LDL cholesterol >3.88 mmol/L (150 mg/dL) to ≤4.40 mmol/L (170 mg/dL), simvastatin 10 mg/day was initiated. If on repeat testing LDL cholesterol was >3.10 mmol/L (120 mg/dL), the dose of simvastatin was increased to a maximum of 20 mg/day. If a patient's LDL cholesterol level was consistently >3.36 mmol/L (130 mg/dL) on subsequent testing, the simvastatin and blinded medication were permanently stopped, and the patient was referred to his or her primary care physician for appropriate treatment. (Although the participant was no longer taking the ACCORD lipid medications, he or she continued to be treated in the glycemia trial and was followed for events.) In a slight revision to the lipid protocol in September 2001, and to minimize confusion in clinics, the LDL cholesterol threshold for uptitration was standardized to 3.10 mmol/L (120 mg/dL) only (Table 1).

To include patients in the trial who were taking lipid-lowering medications at baseline and not have to wash out clinically indicated medications, an algorithm was developed that used the measured on-treatment LDL cholesterol level together with the expected percentage reduction of LDL cholesterol resultant from the pretrial drug and dose to estimate the LDL cholesterol level that would have been caused by discontinuing the treatment. This is listed in Table 2. If the estimated "off-treatment" LDL cholesterol level was <4.40 mmol/L (170 mg/dL), the patient was LDL eligible for randomization, and the dose of simvastatin provided was that appropriate for the patient's estimated LDL cholesterol, as described previously.

AFCAPS/TexCAPS (with a statin)[9] and VA-HIT (with a fibrate)[10] had shown the efficacy of pharmacologic management in subsets of the populations with low HDL cholesterol concentrations. In ACCORD, to select a population of patients at increased risk for CVD due to low HDL choles-

Table 2
Low-density lipoprotein cholesterol (LDL-C) eligibility ranges for screenees taking lipid-lowering agents (by agent and dose), from November 21, 2003, protocol

Lipid-Lowering Agent	Dose (mg)	Estimated % LDL-C Reduction	LDL-C Eligibility Range (Inclusive)	
			mg/dL	mmol/L
Atorvastatin	2.5	25	64–128	1.65–3.30
Atorvastatin	5	29	60–121	1.56–3.12
Atorvastatin	10	39	52–104	1.34–2.68
Atorvastatin	20	43	48–97	1.25–2.51
Atorvastatin	40	50	43–85	1.10–2.20
Atorvastatin	80	60	34–68	0.88–1.76
Simvastatin	5	26	63–126	1.63–3.25
Simvastatin	10	30	60–119	1.54–3.08
Simvastatin	20	38	52–105	1.36–2.73
Simvastatin	40	41	50–100	1.30–2.59
Simvastatin	80	47	45–90	1.17–2.33
Lovastatin	10	18	70–139	1.80–3.60
Lovastatin	20	24	65–129	1.67–3.34
Lovastatin	40	30	60–119	1.54–3.08
Lovastatin	80	40	51–102	1.32–2.64
Pravastatin	10	22	66–133	1.72–3.43
Pravastatin	20	32	58–116	1.50–2.99
Pravastatin	40	34	56–112	1.45–2.90
Pravastatin	80	40	51–102	1.32–2.64
Fluvastatin	20	22	66–133	1.72–3.43
Fluvastatin	40	24	65–129	1.67–3.34
Rosuvastatin	5	40	51–102	1.32–2.64
Rosuvastatin	10	46	46–92	1.19–2.37
Rosuvastatin	20	52	41–82	1.06–2.11
Rosuvastatin	40	55	38–77	0.99–1.98
Rosuvastatin	80	58	36–71	0.92–1.85
Ezetimibe	10	17	71–141	1.83–3.65
Fenofibrate	Any	5	81–162	2.09–4.18
Niacin	Any	10	77–153	1.98–3.96
Resin	Any	10	77–153	1.98–3.96
All others	Any	0	85–170	2.20–4.40

Reflects the off-treatment LDL-C entry criterion of 85–170 mg/dL (2.20–4.40 mmol/L), later altered by the August 31, 2004, protocol, which broadened LDL-C entry criteria to 60–180 mg/dL (1.55–4.65 mmol/L).

terol, who would likely benefit most from HDL increases, patients whose HDL cholesterol was ≥1.29 mmol/L (50 mg/dL) were excluded during the vanguard phase (Table 1). In addition, patients were excluded if their serum concentrations of fasting triglycerides were >8.47 mmol/L (750 mg/dL) (>4.52 mmol/L [400 mg/dL] if receiving fibrate or niacin treatment), because such patients would be at increased risk for developing pancreatitis as a result of uncontrolled hypertriglyceridemia if randomized to placebo rather than fenofibrate.

Safety of combination therapy: At the time of the development of the ACCORD lipid trial's vanguard protocol, the scientific community had considerable concern about the combined use of a statin and a fibrate.[3,4] This concern was reinforced (and the importance of the proposed study design heightened) toward the end of the vanguard phase, when Bayer (Leverkusen, Germany) withdrew cerivastatin from the market (and thus terminated the LDS prematurely) because of an excess of episodes of rhabdomyolysis in the community at large, particularly when it was used in conjunction with gemfibrozil (August 2001).[19,20] Thus, assurance of the safety of the combination of simvastatin and fenofibrate was of great importance. To this end, the investigators decided that the maximum dose of simvastatin should be 20 mg/day.

To ensure patient safety, the frequency and severity of muscle symptoms were monitored at every clinic visit, and creatine phosphokinase (CPK) concentrations were measured at baseline, 4 months, 8 months, 12 months, and annually thereafter and as needed for moderate to severe unexplained muscle symptoms. Through the ACCORD Data and Safety Monitoring Board (DSMB), the frequency and severity of reported muscle symptoms and the frequency of CPK elevations with and without symptoms were monitored by treatment group. Also, patients were withdrawn from lipid-lowering therapy for CPK >10 times the upper limit of normal in the absence of symptoms or for CPK >5 times the upper limit of normal in the presence of symptoms. In addition, simvastatin therapy was to be avoided in participants who developed myositis while taking blinded medication.

As another safety measure, if the triglyceride level was >8.47 mmol/L (750 mg/dL) on 2 consecutive visits (even after adherence review and dietary counseling), the 2 lipid medications (simvastatin and the blinded medication) were stopped, and again, the participant's private physician was notified so that appropriate private lipid-lowering therapy might be initiated. Also, if a patient's LDL cholesterol became <1.29 mmol/L (50 mg/dL), the statin dose was titrated down by 50%, because the safety of very low levels of LDL cholesterol has not been clearly established.

Main trial protocols (January 2003 to the present)—changes necessitated by new evidence: The results of the Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study (HPS) were reported in July 2002.[21] This was a randomized, double-blind, placebo-controlled clinical trial testing whether simvastatin 40 mg/day reduced the risk for all-cause mortality and cardiovascular events in 20,536 high-risk patients (including 5,963 with diabetes)[22] treated over 5 years. The low baseline total cholesterol exclusion criterion (>3.49 mmol/L [135 mg/dL]) resulted in enrollment of many patients with LDL cholesterol concentrations <2.84 mmol/L (110 mg/dL). Most importantly, the HPS showed that simvastatin reduced clinical events by about 25%, even in participants with baseline LDL cholesterol <2.59 mmol/L (100 mg/dL).

The results of the HPS, together with the complexity of the statin treatment in the vanguard phase, led the ACCORD investigators to eliminate statin titration from the main trial and postvanguard portion of the trial and to treat all participants with simvastatin 20 mg/day (Table 1). That is, no participants were left untreated with the statin. This strategy necessitated a change in the eligibility criteria, because if all patients were to be treated with simvastatin 20 mg, it was necessary to protect patients from reductions in LDL cholesterol concentrations to unacceptably low levels. In the revision of the protocol adopted on November 14, 2002, a lower inclusion level for LDL cholesterol of 2.20 mmol/L (85 mg/dL) was adopted. Furthermore, the statin was discontinued if LDL cholesterol decreased to <1.03 mmol/L (40 mg/dL); blinded fibrate or fibrate placebo could be continued.

In April 2004, the results of PROVE-IT–TIMI 22 were reported.[13] This was a randomized, blinded clinical trial that compared the 2-year cardiovascular event rate caused by an aggressive LDL-lowering strategy (atorvastatin 80 mg/day, on-treatment LDL cholesterol 1.60 mmol/L [62 mg/dL]) with that caused by a less aggressive strategy (pravastatin 40 mg/day, LDL cholesterol 2.46 mmol/L [95 mg/dL]) in the setting of an acute coronary event (acute MI or high-risk unstable angina) within the preceding 10 days.[13] In this very high risk population (20% event rate in the first year), there was a 16% reduction in the hazard ratio favoring the more aggressive strategy ($p = 0.005$). However, this trial did not show that the achievement of a marked reduction in LDL cholesterol was superior to the achievement of the ATP III prescribed guideline of <2.59 mmol/L (100 mg/dL), because the less aggressively managed group was not titrated to an LDL cholesterol goal of <2.59 mmol/L (100 mg/dL).

The results of PROVE-IT–TIMI 22 supported the recommendations of the ATP III "implications" report of July 2004, which suggested that, for patients at "very high risk," including those with acute coronary events and those with diabetes combined with coronary disease, an optional LDL cholesterol goal of <1.81 mmol/L (70 mg/dL) could be considered.[23] Subsequently, the TNT trial confirmed the benefit of achieving a target LDL cholesterol level <2.59 mmol/L (100 mg/dL) (mean on-treatment LDL cholesterol 1.99 mmol/L [77 mg/dL]) rather than a target of 2.59 mmol/L (100 mg/dL) in patients with coronary disease.[14] These studies and recommendations increased the pressure to achieve lower LDL cholesterol levels in ACCORD and increased sensitivity to the importance of lowering LDL cholesterol to <2.59 mmol/L (100 mg/dL).

Another important development was the observation of differences between fibrates in their pharmacologic interactions with statins. Whereas the coadministration of gemfibrozil with various statins increased the area under the statin serum concentration curve, no such effect was observed when fenofibrate was coadministered with a statin.[20] This difference has been demonstrated to be caused by the inhibition of acid glucuronidation of statins by gemfibrozil.[24] This body of research lessened concern that the coadministration of simvastatin with fenofibrate would result in excess muscle adverse events.

The conjunction of evidence that patients at high risk should achieve LDL cholesterol <2.59 mmol/L (100 mg/dL) and that the combination of fenofibrate with a statin possibly posed no greater risk than expected from the additive effects of either drug alone, together with the safety experience with the combination of fenofibrate and simvastatin 20 mg in the vanguard phase and early phase of the main trial, prompted the ACCORD investigators to modify the lipid management strategy (August 2004 protocol) so that simvastatin should be titrated up to 40 mg if the LDL cholesterol level remained consistently >2.59 mmol/L (100 mg/dL) (Table 1). (Extending this notion of who should be taking simvastatin 40 mg, the May 2005 protocol mandated that all secondary prevention participants in the lipid trial should also receive this higher dose.) Given that a strategy was in place for the discontinuation of the statin if LDL cholesterol decreased to <1.03 mmol/L (40 mg/dL), the inclusion criteria for trial eligibility were also broadened in August 2004 to include patients with LDL cholesterol of 1.55–4.65 mmol/L (60–180 mg/dL).

It is expected that this algorithm for simvastatin treatment will provide an average LDL cholesterol in the lipid portion of ACCORD that will be well below 2.59 mmol/L (100 mg/dL) and that only a very small percentage of patients will have LDL cholesterol concentrations >2.59 mmol/L (100 mg/dL). Additionally, the protocol was changed in August 2004 so that an LDL cholesterol level

>3.10 mmol/L (120 mg/dL) with simvastatin 40 mg would lead to the discontinuation of the blinded medication and the transfer of care to the patient's private physician for the appropriate therapy for LDL cholesterol.

Another modification of the protocol dealt with a slight elevation of serum creatinine levels associated with fenofibrate use. After observing that some lipid trial participants had experienced increases in serum creatinine after randomization to blinded fenofibrate or placebo therapy, the ACCORD investigators noted published research suggesting an association of uncertain significance between fenofibrate use and increases in serum creatinine concentrations.[25,26] At least 1 report suggested that the increase in creatinine associated with fenofibrate use was not associated with a deterioration of renal function, and the effect was determined to be rapidly reversible.[26] However, in the course of researching this question, the manufacturer's recommendation that the dose of fenofibrate be reduced or discontinued in patients with impaired renal function was noted, and for the purpose of safety and to avoid the accumulation of metabolites, the protocol was changed in August 2004 so that the dose of blinded medication was to be titrated down on the basis of the patient's estimated glomerular filtration rate (GFR). Specifically, the fenofibrate (or matching placebo) dose is titrated to 54 mg/day if the estimated GFR consistently ranges from 30 to <50 mL/min per 1.73 m^2 and discontinued if the estimated creatinine clearance is consistently <30 mL/min per 1.73 m^2.

Finally, to increase the numbers of women and minorities in the study, and recognizing that women and African Americans with diabetes tend to have CVD despite higher HDL cholesterol concentrations than others, the entry HDL cholesterol criteria were changed so that women or African Americans with HDL cholesterol <1.42 mmol/L (55 mg/dL) were eligible for the study, whereas all others were required to have HDL cholesterol <1.29 mmol/L (50 mg/dL).

Conclusion

One of the most important questions that could be asked about the pharmacologic management of dyslipidemia in patients with diabetes is whether combined therapy with a statin plus a fibrate offers an additional reduction of cardiovascular events beyond that of a statin alone, with an acceptable risk profile. The importance of this question is highlighted by the recent Simvastatin Plus Fenofibrate for Combined Hyperlipidemia (SAFARI) trial, evaluating lipid responses and the safety of combination therapy as opposed to a statin alone.[27] This study showed a statistically significant benefit of the combination therapy in reducing LDL cholesterol and triglycerides and increasing HDL cholesterol with similar clinical, muscular, and liver adverse experiences over 12 weeks in 619 patients with combined hyperlipidemia. ACCORD will address these issues, as well as the issue of clinical outcomes in patients with diabetes.

The original design of the lipid component of ACCORD was made after considerable deliberation. However, during the first 5 years of the trial, the results of several major clinical trials, including HPS,[21] PROVE-IT–TIMI 22,[13] and TNT,[14] and expert lipid panelists' recommendations (NCEP ATP III,[4] Grundy et al[23]) led to significant modifications in the ACCORD lipid trial study design. In addition, there were 2 important developments relating specifically to the use of fenofibrate in the trial. One supported the greater safety of fenofibrate than gemfibrozil when used in association with a statin,[20] and another highlighted an association of uncertain significance of increasing serum creatinine associated with fenofibrate use.[25,26] Related to this last point are the observations reported in 2005 from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, which compared fenofibrate therapy with placebo (in the absence of specifically mandated LDL cholesterol–lowering therapy) in 9,795 patients with type 2 diabetes to assess the effect of the fibrate on CVD events.[28] In that trial, although an 11% reduction in total cardiovascular events (a secondary outcome; $p = 0.035$) was observed, it was also noted that during the course of the 5-year trial, median plasma creatinine levels remained about 11 μmol/L (0.1 mg/dL) higher in the fenofibrate group compared with the placebo group. In a subset of patients restudied 8 weeks after the discontinuation of the study medication, the median plasma creatinine in the fenofibrate participants decreased to a level observed in those assigned placebo.[28]

The ACCORD investigators were sensitive to the clinical implications of these developments and revised the protocol accordingly. In each case, the potential benefit of a modification of the treatment regimen was balanced against the potential toxicity of the combination of a statin and a fibrate. Overall, ACCORD has been able to proceed through several iterations of the original lipid trial design. The current study protocol meets the standards of present optimal care on the basis of evidence from clinical trials, without jeopardizing our ability to detect differences in important outcomes.

Of obvious concern at every step of protocol revision is the effect of protocol change on the power of the trial to answer the research questions. This applies to the smaller lipid trial and the overarching glycemia trial. However, the changes that have been made from the first vanguard protocol (October 2000) to the current protocol (May 2005) have not had any large effect on power. Specifically, it was stated in the October 2000 protocol that the glycemia trial had 92% power and the lipid trial had 90% power to answer their respective questions. In the May 2005 protocol, these had been reduced to 89% and 87%, respectively.

The designs of major clinical trials of long durations are likely to be significantly affected by changes in knowledge and treatment recommendations over the life of the trials, as evident from ACCORD. Sponsors of such trials should

anticipate the need for changes in the protocols in response to evolving evidence, which will have significant operational implications in terms of budgets, the need for periodic updating of patient consent, and the power of large trials to test their prespecified hypotheses.

1. Goff DC, Gerstein HC, Ginsberg HN, Cushman WC, Margolis KL, Byington RP, Buse JB, Genuth S, Probstfield JL, Simons-Morton DG, for the ACCORD Study Group. Prevention of cardiovascular disease in persons with type 2 diabetes mellitus: current knowledge and rationale for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Am J Cardiol* 2007;99(suppl):4i–20i.
2. ACCORD Study Group. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. *Am J Cardiol* 2007; 99(suppl):21i–33i.
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993;269:3015–3023.
4. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285: 2486–2497.
5. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389.
6. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E, for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; 335:1001–1009.
7. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339: 1349–1357.
8. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; 333:1301–1307.
9. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS [Air Force/ Texas Coronary Atherosclerosis Prevention Study]. *JAMA* 1998;279: 1615–1622.
10. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J, for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999;341:410–418.
11. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; 317:1237–1245.
12. Robins SJ, Rubins HB, Faas FH, Schaefer EJ, Elam MB, Anderson JW, Collins D, for the Veterans Affairs HDL Intervention Trial (VA-HIT). Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes Care* 2003;26:1513–1517.
13. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM, for the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–1504.
14. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK, for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425–1435.
15. MacMahon M, Kirkpatrick C, Cummings CE, Clayton A, Robinson PJ, Tomiak RH, Liu M, Kush D, Tobert J. A pilot study with simvastatin and folic acid/vitamin B_{12} in preparation for the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). *Nutr Metab Cardiovasc Dis* 2000;10: 195–203.
16. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Palmer G, for the Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group. Design and baseline characteristics of the Incremental Decrease in End Points Through Aggressive Lipid Lowering study. *Am J Cardiol* 2004;94:720–724.
17. Steiner G. Lipid intervention trials in diabetes. *Diabetes Care* 2000; 23(suppl):B49–B53.
18. Elam MB, Hunninghake DB, Davis KB, Garg R, Johnson C, Egan D, Kostis JB, Sheps DS, Brinton EA. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT [Arterial Disease Multiple Intervention Trial] study: a randomized trial. *JAMA* 2000;284:1263–1270.
19. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002;346:539–540.
20. Alsheikh-Ali AA, Kuvin JT, Karas RH. Risk of adverse events with fibrates. *Am J Cardiol* 2004;94:935–938.
21. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360: 7–22.
22. Collins R, Armitage J, Parish S, Sleigh P, Peto R, for the Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;361: 2005–2016.
23. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ, for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *J Am Coll Cardiol* 2004;44:720–732.
24. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos* 2002;30:1280–1287.
25. Hottelart C, El Esper N, Rose F, Achard JM, Fournier A. Fenofibrate increases creatininemia by increasing metabolic production of creatinine. *Nephron* 2002;92:536–541.
26. Hottelart C, el Esper N, Achard JM, Pruna A, Fournier A. Fenofibrate increases blood creatinine, but does not change the glomerular filtration rate in patients with mild renal insufficiency [in French]. *Nephrologie* 1999;20:41–44.
27. Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for com-

bined hyperlipidemia (the SAFARI trial). *Am J Cardiol* 2005; 95:462–468.
28. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, et al, for the FIELD Study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849–1861.

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† Deceased.