Foreword

From the Editor: An interview with Dr. Scott Grundy

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Abstract: During the American Heart Association’s Scientific Sessions in November 2014, this Editor had the opportunity to interview Dr. Scott Grundy regarding the new recommendations for guideline development that was issued by the International Atherosclerosis Society. (The full document is published in this issue of the journal). In developing this report, Dr. Grundy chaired a panel of international experts who spent 1 year in consideration of new evidence and regional concerns regarding the clinical management of lipoprotein disorders and vascular disease prevention. His experience in developing the Adult Treatment Panel Reports from the National Cholesterol Education Program in the United States and his extensive research in lipoprotein physiology and related disorders makes him unique in offering the expertise for worldwide leadership in this effort.

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Dr. Brown: Dr. Grundy, why do you feel it’s helpful to have an international perspective on guidelines for managing dyslipidemia? Are not the conditions in the various nations so different that recommendations may not be generally applicable?

Dr. Grundy: It is true that conditions are different in different countries, so if you’re going to make a general guideline, you have to be flexible. In our process of making these guidelines, we had representatives from all the nations in the world, and some of them pointed that out very clearly that some of the things that we were recommending didn’t exactly fit with their own national recommendations or with their own views. So, we did our best to adjust for their comments of variability, but overall, I think we came up with a balanced guideline that can be used in almost all countries of the world.

Dr. Brown: Why did the International Atherosclerosis Society (IAS) choose to issue recommendations as an update of previous guidelines? Why is it appropriate to do that at this time?

Dr. Grundy: Previous guidelines had actually focused on bringing together other guidelines, trying to harmonize them, but the feeling was that the IAS has a special interest in dyslipidemia. And because the previous guidelines are also quite old, the feeling was that a lot has happened in the field in the past 10 years, so we should bring our guidelines up to date, and in particular, focus on the dyslipidemia problem.

Dr. Brown: You mentioned that you had representation from across the world. What were the criteria for the individuals who participated on your committee?

Dr. Grundy: The people on the committee were selected by the IAS Board. The IAS Board members certainly know the major players in the world. The criteria were a wide range of representation throughout the world and expertise in the lipid area or atherosclerosis; those were the two major criteria. We also wanted other types...
of representation to make sure that the panel was well-balanced. The Board paid very close attention in the selection of the people.

Dr. Brown: During your discussions, I’m sure these individuals brought forth specific differences in their populations. I was wondering if you’d give us some examples of issues where you found discontinuity between Western guidelines in the United States or Europe and other areas of the world where the populations are so different.

Dr. Grundy: One example has to do with the population in Japan. There are several articles from Japan indicating that triglycerides are more important than low-density lipoprotein (LDL) as a risk predictor. Maybe the reason is that the Japanese tend to have relatively low levels of LDL to begin with. In China, there is a fairly low risk for coronary heart disease compared with the United States; but there’s a high prevalence of stroke in China, so the feeling was that we needed to pay as much or more attention to stroke. Then, another factor to consider was risk assessment. The baseline risk for coronary heart disease differs in different populations. For example, in China, the risk is lower than it is in the United States, all other things being equal. There’s just something about the Chinese population that makes their risk lower, whereas in Korea—for some other reason that we don’t fully understand—the baseline risk of the population is higher. So, we tried to put adjustments into the risk assessment to take that into account. Fortunately there’s quite a bit of data available on that point.

Dr. Brown: In writing the guidelines, did you find that LDL cholesterol (LDL-C) continued to be the dominant theme around the world, in terms of both risk assessment and as a target of treatment?

Dr. Grundy: That’s a very interesting question. What came out as we progressed was that there’s a growing interest in adding very LDL (VLDL) to LDL to make non–high-density lipoprotein (HDL). So, non-HDL cholesterol really has emerged in the past few years as probably a better marker of risk and a better target of treatment. There was some discussion about whether it would be better to emphasize mainly LDL or switch more to non-HDL.

In the final analysis—and I was somewhat surprised about this—the majority of the panel wanted us to emphasize non-HDL more than LDL. Although others felt that LDL is so fixed in everybody’s mind, to make a change like that might be a little confusing to people, but non-HDL is coming into its own.

Dr. Brown: I know that the Scandinavians and Northern Europeans have felt that triglyceride gave a message that seemed to be stronger than we, in America, had determined from our community-based studies. They’ve always been very interested in dealing with the triglyceride problem. Were they satisfied with non-HDL cholesterol incorporating this issue adequately?

Dr. Grundy: We had representation and they approved it. I don’t know, specifically, that the Scandinavians brought this question up for detailed discussion, but if you look at everybody throughout the world, all of our representatives felt that VLDL is increasingly important.

There is something that I have to mention, though, and that is that there are national guidelines. The European Atherosclerosis Society has recently published a new dyslipidemia guideline for Europe. Some of the people from Europe were a little squeamish about supporting IAS recommendations that might interfere with their new guidelines. I read them very carefully and I’m very impressed with what they’ve done: very thoughtful, thorough, and reasonable, so they’re very good. I can understand that they would not want the IAS to supersede the European guidelines.

However, that said, I think that they will have an influence in Europe because of certain unique things that were added into the IAS recommendations. Overall, I believe the IAS recommendations will be well received in the major areas of the world, such as China, India Southeast Asia, the Middle East, and Latin America. So, we believe that there are plenty of people in the world who will read these guidelines and buy into them.

Dr. Brown: I agree with you. I also have studied those European guidelines and they’re very thorough. They’re an education for any physician regarding both risk assessment and choosing both targets and goals of treatment. On the other hand, there is so much information that it brought to mind the old saying that perfection can be the enemy of success. So, I think one of the cries has been for simplifying the guidelines so that they can be applied quickly in practice when you’re having a visit with a patient.

Dr. Grundy: I agree with that. Certainly, we tried to make our guidelines as simple as possible and to have an executive summary that summarizes our recommendations. I believe from the executive summary alone that the guidelines can go a long way in their practice. If you want some more details, you can go to the full report, but again, it is not as detailed as the European guidelines.

Dr. Brown: I’ll point out that the executive summary was published in the December issue of the Journal of Clinical Lipidology and the full report is in this issue.

Now, I would like to ask you about the process of developing your report. What were the essential sources of information that you considered in synthesizing the totality of the evidence that underlie your recommendations for these approaches to guideline development?

Dr. Grundy: We took the view, which was actually the view in the previous American Adult Treatment Panel guidelines, that we should look at all the evidence. We should look at clinical trials—they should certainly be high on the priority list—but we should also examine the vast amount of epidemiological evidence, for which there are no clinical trials. Examples of the latter include Asia and Latin America. There’s a lot of epidemiology that tells us important information about cholesterol and heart disease and stroke. So we did not restrict ourselves to randomized, controlled clinical trials.

We certainly gave them their full due and, where possible, we emphasized them. But then, there are a lot of other kinds of information. There are genetic studies, such as familial hyperlipidemias. There are even animal studies and
in vitro studies. But epidemiology and clinical trials were the major sources of information.

**Dr. Brown:** There is, from all these sources, a rather substantial and well-documented theory about how atherosclerosis actually develops at the tissue level. As you say, that has been generated from many, many different sources. What would you say are the crucial issues about that theory and how do they go to the guidelines?

**Dr. Grundy:** Well, we have more than 50 years of studies in this field, which has produced a vast amount of data. There has been the thought—and I think I agree with it—that when you look at all the data, certain principles come forward. The key principle was that the atherogenic lipoproteins—LDL and non-HDL—are the major drivers of atherosclerosis. Everybody knows that there’s a lot of cholesterol in plaques and that cholesterol comes from the bloodstream, from atherogenic lipoproteins. What we’ve learned in the past 10 or 15 years is that not only do cholesterol-rich lipoproteins start atherosclerosis, but they play a role right up to the time of heart attack. Somehow they promote inflammation in the artery wall that predisposes plaques to rupture. This has been demonstrated by the clinical trials that show you can get very quick reduction in risk by lowering LDL levels.

The theory is that atherogenic lipoproteins are the driving force of atherogenesis. But in addition, other risk factors, such as hypertension, smoking, and obesity, metabolic syndrome, and diabetes accelerate atherogenesis or predispose to plaque rupture. That’s the overall theory of the pathogenesis of atherosclerotic disease. I believe it has a very strong foundation.

**Dr. Brown:** Are there any new genetic data that tend to support this hypothesis or detract from it?

**Dr. Grundy:** The genetic data do support the basic theory that you mention. Most dramatic is familial hypercholesterolemia, where people have very high LDL levels. We know that you can develop atherosclerosis and coronary heart disease without any other risk factors. In fact, if LDL levels are high enough, as occurs in patients with homozygous familial hypercholesterolemia; little children can have heart attacks and with no other risk factors. They don’t smoke. They don’t have high blood pressure. They don’t have diabetes. So, that proves that high cholesterol alone can cause atherosclerosis and heart attacks.

There are several genetic forms of dyslipidemia, and many of them are accompanied by increased risk; examples are familial combined hyperlipidemia, familial dysbetalipoproteinemia, and familial defective apoB. All of these other genetic dyslipidemias impart an increased risk.

Very recently, there’s been another exciting genetic issue. There is a protein in the blood called PCSK9 that blocks the LDL receptor, raises LDL levels. Rare people have a mutation in this protein resulting in low LDL levels over a lifetime. Because of low LDL levels, affected persons rarely get coronary heart disease. This is 1 of the most exciting recent findings in the field, and once again, points to the importance of atherogenic lipoproteins.

**Dr. Brown:** It seems that it is the gradient between the concentration of apoB-containing lipoproteins in the bloodstream and the tissues that really drives atherosclerosis.

**Dr. Grundy:** Without a doubt.

**Dr. Brown:** That sets the stage for the logic of much of our therapy in the past; that is, to lower that gradient, lower the concentration in the plasma. There are many lines of evidence that support both incidence of clinical disease being related to the height of that gradient and the lowering of that gradient producing a very beneficial effect on atherogenesis.

**Dr. Grundy:** Yes.

**Dr. Brown:** Is there information from those developing new lipid-lowering drugs that were considered in these recommendations that you’ve made—drugs that may be in development that show great promise?

**Dr. Grundy:** All I can say, if the drugs are not yet available, we couldn’t recommend them, of course. But hopefully, they will be available soon. At present, those suppressing PCSK9 concentrations seem to be the most promising.

**Dr. Brown:** Most of our previous drugs have changed the way LDL is cleared from the blood by accentuating the population of LDL receptors on the liver cell surface. Now, with these new drugs, there is the promise that we will have drugs that will work by different mechanisms, but all of them lower the gradient of LDL or apoB-containing lipoproteins between artery wall and plasma space. Is that correct?

**Dr. Grundy:** That is correct. There are drugs now that have been developed and are available on a limited basis that work in another way; namely, they interfere with the formation of atherogenic lipoproteins. These are drugs such as microsomal triglyceride transfer protein inhibitors and RNA antisense drugs. They reduce the liver’s secretion of apoB-containing lipoproteins. These drugs are also LDL-lowering drugs. They have been approved for severe hypercholesterolemia as orphan drugs. At the very least, they point to the potential for lowering LDL in other ways besides through the receptor mechanism.

**Dr. Brown:** There have been a number of important clinical trials. It seems that 1 of the most important general messages that we’ve received from those is that we can reduce apoB-containing lipoproteins quite dramatically without direct consequences from that process. Without adverse effects directly from the drug, LDL reduction seems to have no lower limit with regard to safety. Do you have a feeling about where that’s leading us in terms of setting potential targets for LDL or apoB-containing lipoproteins?

**Dr. Grundy:** First of all, there’s the question of whether it is possible to lower the LDL so much that we create danger. To date this has not happened. Some of the epidemiology studies suggest that people who have very low cholesterol levels may be at increased risk for hemorrhagic stroke; but if so, this has not shown up in any of the clinical trials. The mechanism by which brain hemorrhage might occur is not clear either. So right now, I would say that there is no dangerously low level of LDL.

With that said, there is a very rare condition called abetalipoproteinemia, in which no LDL can be detected in
the circulation. Consequently no lipoproteins are available to transport vitamin E to the nervous system; such an abnormality can produce some neurological problems. On the other hand, rare patients have a condition called hypobetalipoproteinemia. They tolerate very low levels of LDL very well and don’t seem to have significant side effects.

So, I would say, from a therapeutic point of view, we’ve come to the conclusion that to prevent ASCVD the lower, the better for LDL. That’s a bit of a catch phrase, but it is probably correct. We will know for sure when anti-PCSK9 drugs are fully tested.

Dr. Brown: Most of our clinical trial data have come from the statin group of drugs. They, clearly, are the most popular drugs and have made a huge impact on medical care around the world. Some of the more recent trials have succeeded in lowering LDL-C quite dramatically, many patients well below 50 mg/dL.

In the face of that, what did the committee think about simply giving maximum doses of statins and attempting to achieve the lowest LDL possible in everybody? Did you discuss that?

Dr. Grundy: Well, yes. Some people are thinking seriously about this approach. There’s a clinical trial called JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), in which patients entered with fairly low LDL levels to begin with. They were given what might be called a hefty dose of rosuvastatin, a powerful LDL-lowering drug. On this drug, the LDL came down to about 60 mg/dL, and treated patients had a dramatic reduction in risk for cardiovascular events over a short period. It was so dramatic that the monitoring committee thought it inappropriate to continue because benefit was clearly demonstrated. So, there is a theoretic rationale for taking a very aggressive approach to cholesterol. Still, many people worry about the side effects of statins. That’s an important issue in itself, but there’s nothing wrong with that idea in theory. I’m not sure the medical community is quite ready for widespread use of high-intensity statins in the population. But we can see from the new American College of Cardiology/American Heart Association (ACC/AHA) guidelines that expanding use of statins is advocated.

Dr. Brown: I noticed that the committee has continued to believe that it’s appropriate for physicians to have a goal in mind when they treat LDL or apoB-containing lipoproteins and to adjust therapy to achieve a goal.

What are the advantages of doing that, as opposed to simply just giving people a high dose of statin?

Dr. Grundy: Now, for secondary prevention, thanks to several clinical trials, we know that if you lower the LDL down to very low levels—in the range of 70 to 80—you get enhanced risk reduction. So we defined an optimal LDL-C for secondary prevention to be less than 70 mg/dL. This optimal level is based on several lines of evidence: randomized clinical trials (RCTs), subgroup analysis of RCTs, population epidemiology, and genetic epidemiology.

We believe that this level is a reasonable goal for secondary prevention. Interestingly, the new ACC/AHA guidelines recommended that patients with established atherosclerotic cardiovascular disease (ASCVD) be given high-intensity [high-dose statins]. It is true that the best RCTs in secondary prevention used high-dose statins. The IAS panel noted, however, that many patients with ASCVD do not achieve a very low LDL-C on high-dose statins. For such patients, we left the door open to further LDL reduction through addition of a second LDL-lowering drug.

For primary prevention, the IAS panel identified an optimal LDL-C to be <100 mg/dL. This was not a required goal for everyone, but the evidence is strong that if a person sustains an LDL-C of <100 mg/dL over a lifetime, the incidence of ASCVD will be low. This optimal level was obtained by examining data of RCTs, subgroup analysis of RCTs, population epidemiology, and genetic epidemiology. For example, people who have PCSK9 mutations have lifetime levels of LDL-C in the range of 100 mg/dL. Even into their 60s, they have almost no ASCVD. Further, in populations around the world where LDL-C levels are in this range, ASCVD is relatively rare. So the panel decided that any level of LDL-C <100 mg/dL, if maintained for a lifetime, would be associated with a low rate of ASCVD. Of course, in older, high-risk patients who have had a relatively high LDL throughout life, a greater benefit can be achieved by still lower LDL-C concentrations. This was shown in the JUPITER trial. But if a person can keep his or her LDL-C below 100 mg/dL throughout life, chances of developing ASCVD are relatively low.

Dr. Brown: The other issue that the clinician has to face is that individual patients, as opposed to clinical trial populations, have quite varied responses to statin therapy. Some have dramatic reductions of 70% to 80%, and others with the same dose of the statin may only have a 10% to 20% reduction.

What was the committee’s feeling about how you deal with that issue? What are your alternatives to the patient with an inadequate response and what did you recommend?

Dr. Grundy: We opened the door to using drugs in combination to enhance LDL-lowering. If a patient fails to attain the desired reduction of LDL-C on a statin, it is entirely reasonable to add a second LDL-lowering drug.

I will admit that there have not been adequate clinical trials that look at all different possible drug combinations and all different levels. These just don’t exist, and I doubt that they ever will exist. It is unrealistic to carry out so many trials. But the many lines of evidence for a causal relationship between LDL and ASCVD risk led our panel to the conclusion that further lowering of LDL by addition of a second drug will reduce risk. Of course, small reductions may not produce much more in risk reduction, so clinical judgment is needed when making a decision to add another lipid-lowering drug. Currently available non-statin drugs are not particularly powerful. The real test of the efficacy of additional cholesterol-lowering will come when anti-PCSK9 drugs are added to statins.
Dr. Brown: The tradition has been to use the cholesterol content of LDL as our marker, and in great part that came about because we simply had methodology to make that measurement. In clinical trials, we have measured relationships with LDL-C change in a retrospective sense; for the most part, very few trials have actually treated to some target value in the intervention group.

There are retrospective analyses with other markers, not just LDL-C in these trials, and yet, they seem to not achieve the significant recognition by recent committee action and in recent guidelines. You’ve already raised 1, non-HDL cholesterol, which in this type of analysis seems to be, at least, as strong as LDL as an indicator, not only of risk, but also of success in treatment. It correlates with reduction in events in large trials.

The other marker that has been touted, which goes to this issue, is apoB. Did you discuss apoB as a potential marker?

Dr. Grundy: We did. Some committee members really like apoB and thought that we should incorporate it into the guidelines. So we gave a nod to apoB. Of course, if you look at many of the countries of the world for which these guidelines were created, apoB measurements are not readily available. We tried to simplify the guidelines as much as possible. Nonetheless, apoB would be a very good marker for response to LDL-lowering therapy. I, personally, have some questions about standardization of the apoB measurement. That’s just my personal opinion and not everyone agrees. But the potential of utility of apoB is there.

Dr. Brown: I have learned something very interesting in my discussions with a scientist from the Centers for Disease Control and Prevention. As you know, that laboratory is the mecca for standardizing lipid measurement systems in the United States. It turns out that the precision and accuracy of apoB measurement is better than LDL-C in many laboratories. That may only be true for the United States and it may only be true for the Centers for Disease Control and Prevention Standardization Program, but the message was that in large laboratories where many thousands of samples run daily, the apoB assay turns out to be very precise, accurate, and inexpensive. It should cost very little more than measuring LDL-C. So it may be that it’s possible to adopt that in the future if it offers a clinical advantage.

Dr. Grundy: Yes, I think that’s a very good point. I see no reason why we shouldn’t continue to try to improve the accuracy of apoB measurement and its availability.

Dr. Brown: Now, let’s turn to other assessment measures. In the previous guidelines in the United States and in Europe, the metabolic syndrome has been given a lot of attention. We know that there is a population of patients in which LDL-C does not seem to spell out risk in a full way, whereas, if you bring in triglyceride and HDL, you get another picture of risk that enhances that.

What did you decide to do about the clinical designation of the “metabolic syndrome,” and what did you recommend in terms of its incorporation into guidelines?

Dr. Grundy: We strongly recommended that it be incorporated. It provides a way to deal with the metabolic complications of obesity and other metabolic derangements. The metabolic syndrome is mainly a lifestyle issue. If you have metabolic syndrome, you can correct all the metabolic risk factors by weight reduction and exercise. I would say that we emphasized lifestyle change in all our recommendations and particularly in those with the metabolic syndrome.

One of my concerns about these ACC/AHA cholesterol guidelines is that they seem to emphasize drugs almost entirely. This may not be true, because separate guidelines on lifestyle have not been integrated. Maybe when that’s done, a more balanced set of guidelines will be forthcoming. Anyway, our committee came down very strongly on lifestyle, and because of the growing prevalence of obesity around the world, the metabolic syndrome has become really important.

Dr. Brown: The new guidelines that were just published by the ACC/AHA emphasize total cholesterol and HDL in risk assessment, but do not bring triglycerides into the picture. There is a separate set of guidelines on obesity, and in that, weight loss, of course, is highly emphasized. But the risk assessment does not really address the compilation of the consequences of obesity as a special case.

Dr. Grundy: The Adult Treatment Panel III placed increased emphasis on the metabolic syndrome. This syndrome includes obesity and dyslipidemia, among other metabolic risk factors. This syndrome was well accepted by the medical community. Unfortunately, the ACC/AHA guidelines did not reintroduce the metabolic syndrome. Both the AHA and the National Heart, Lung, and Blood Institute had made a major commitment to educational programs with the metabolic syndrome. I believe its importance is well accepted, so maybe there won’t be too much harm in the failure to include it in the new guidelines.

Dr. Brown: We have certainly seen a subpopulation in multiple trials where aggressive statin therapy was used, but who remained with high triglycerides, let’s say higher than 200, and low HDL—well below 40—and those populations seemed to have much higher risk, even during treatment with statins.

Dr. Grundy: You are right about that. High triglycerides are a potential treatment target. In the Action to Control Cardiovascular Risk in Diabetes study, unfortunately, when they added fenofibrate in patients with diabetes, it didn’t turn out too well. But the trial design didn’t select many patients who had elevated triglycerides and low HDL. Still, a subgroup analysis of that trial and several other fibrate trials have reported that people who have high triglycerides and are at high risk, benefit from fibrate therapy. I believe there is a lot of room for research in people with high triglycerides.

Dr. Brown: It seems that 15% or 20% of patients, in males at least and in the older age groups—50 to 60 years old—have this problem. We’ve seen that in the Veterans Administration system. The Veterans Administration recently looked at their
population and found 200,000 patients who had their LDL controlled with statins, but triglycerides were still higher than 200 and HDL less than 40. It seems clear that these are significant risk factors for that health care system to manage. Right now, we don’t have adequate evidence to recommend a specific treatment broadly, but a more definitive study needs to be done.

Dr. Grundy: For many years, our laboratory has studied hypertriglyceridemia. It is still an important clinical problem. In our Lipid Clinic, we get many referrals for elevated triglycerides.

Dr. Brown: That’s right. In fact, you and I published an article together on changing triglyceride synthesis without changing apoB production with a high-carbohydrate diet. Was there discussion in these guidelines or recommendations with regard to diet or was that an issue that was left to a later date?

Dr. Grundy: The IAS guidelines placed a major priority on lifestyle modification. On a worldwide perspective, much more can be gained from improvement of lifestyle than from drug therapy.

Dr. Brown: Perhaps the major enigma that still remains in our field is the problem of low HDL cholesterol. The epidemiology seems to point in 1 direction, but the clinical trials all point in another.

Where do you think we stand with that and what are the general recommendations for HDL in your recommendations?

Dr. Grundy: As you say, HDL has been an enigma. It clearly is related to risk. There’s no question about that. A low HDL level is a risk factor in most populations—maybe not in all populations—but in most. So, this has led to the idea, if we can raise HDL, it might reduce risk. There’s more than 1 way to raise HDL. You can raise it by weight reduction and exercise, and we think that would be beneficial. But clinical trials are lacking. Two currently available HDL-raising drugs are fibrates and nicotinic acid. Both have been tested in clinical trials. There is suggestive evidence of benefit. However, these drugs are not powerful HDL-raising drugs and they also lower LDL and triglycerides. So it is difficult to know whether any benefit is due to HDL-raising. Another class of HDL-raising drugs is the cholesteryl ester transfer protein inhibitor. It is under study, and it is too early to tell whether it will be beneficial.

Dr. Brown: The really confusing part of HDL is that it consists of so many different entities; many different particles with many different proteins and lipids involved in these structures. It seems certain that HDL particles move cholesterol from peripheral tissues to the liver, but there are also many other theories as to its potential benefits.

Dr. Grundy: That’s right. It’s associated with so many different things. I’m seeing articles where it’s strongly associated with insulin resistance, so if you have a low HDL, you’re likely to be insulin resistant. A low HDL is associated with high triglycerides, so you don’t know whether it’s the high VLDL or the low HDL that’s the culprit there.

The HDL is more a reliable, consistent indicator of risk, whereas the triglycerides are more variable; and that’s why low HDL shows up more in epidemiology studies as being a more powerful predictor than triglycerides: but in reality, high levels of triglyceride-rich lipoproteins may be more atherogenic than a low HDL. So, we just don’t know yet. It certainly deserves research, and HDL may turn out to be an important additional factor that we could modify. That would be terrific, if it turns out to be the case.

Dr. Brown: I want to return now to this issue of goal-setting. We have the new recommendations, which emphasize the importance of defining those people who are going to do well with statin therapy. They recommend that physicians not worry about goals of treatment; the issue is to keep them on statins and good outcomes are likely to happen.

What do you see as the pros and cons in terms of clinical management of keeping goals of therapy in the clinical guidelines?

Dr. Grundy: In my opinion, treatment goals have a lot of clinical utility. But recent guidelines have found it difficult to define a clinical goal for LDL. The available data suggest that the lower the better for LDL levels. For secondary prevention, this translates into a goal in the range of less than 70 mg/dL. However, in primary prevention, if the baseline LDL is well above 100 mg/dL, reducing the LDL to <100 mg/dL should be sufficient. On the other hand, if higher risk patients have a low LDL, further LDL lowering to the range of <70 mg/dL will provide additional benefit. This benefit was shown in the JUPITER trial. In low-LDL/high-risk patients, a goal of <70 mg/dL is reasonable.

Dr. Brown: I found it a bit ironic that in considering the value of goals, so much emphasis was placed on clinical trials that tested statins, but did not share the LDL achieved with the physicians or anyone else. By design, they were blinded trials to reduce bias. However, the result was that the patients and physicians continued for 5, 6, 7 years sometimes without knowing what the lipoprotein values were. So, I’m not sure how you learn from such an experiment, as to whether setting and monitoring lipoprotein goals are beneficial tactics or not. They are moot as to a goal achievement, except in a retrospective way. Even there, we see a relationship between the LDL achieved and the reduction. Furthermore, when you take initial risk status into consideration, the trials that have had the greatest differential in LDL reduction show the greatest reduction in event rates. To me, that seemed like confirmation that goal achievement was a beneficial idea.

Dr. Grundy: I agree with that. RCTs are of great value. On the other hand, there simply is not enough information from trials to develop comprehensive guidelines. The authors of the ACC/AHA guidelines pointed this out. It is a major weakness. To flesh out the guidelines and to make them practical, expert judgment is needed. I believe that most clinicians would be pleased to know what the experts think about various issues. This has been my experience.

Dr. Brown: They are consistent with the basic theory of atherosclerosis, as we discussed earlier in this conversation.
The lower the gradient, the lower the atherogenic process should be. Until someone shows me evidence that this theory is wrong—then, it seems to me, that seeking appropriate goals in light of risk provide for an important set of guidance principles that we should continue to follow.

**Dr. Grundy:** One thing that concerns me about giving up recommending goals is that our data in clinical trials come not from a specific focus on the atherogenic lipoproteins. These are considered secondary to the testing of specific drugs used in the clinical trials. They abandon the theory and only look at the drugs.

I think that might work okay if you’re looking at a heart failure drug that’s got to be given for a short period; the test is if it works or it doesn’t work in changing mortality, etc, that makes a lot of sense. But with cholesterol, we’re talking about a lifetime problem and you have to take a different approach. More is needed for guidance for lifetime prevention than a few RCTs with drugs.

**Dr. Brown:** The art of management is extremely important over time. In my experience as a physician, I find that being able to discuss a short-term goal as I prescribe a drug and then to adjust that drug to achieve the goal, seems to ring true with the patient’s concept of prevention. We cannot report on what is actually happening to their arterial disease as we encourage adherence to treatment.

I find it very difficult to believe that simply giving a drug and telling the patient to have faith in this drug and not to worry about what it’s actually doing to the causative factor in their disease would lead to needed long-term adherence.

**Dr. Grundy:** Well, I think the adherence is really going to be the crux of the problem. If you don’t monitor where you stand with lipid-lowering therapy and the physician is not paying attention, then adherence is going to fall off. We know that.

**Dr. Brown:** The data strongly suggest that patients are often given a prescription for a statin, the dose isn’t adjusted, and on the return for their annual visit half of them aren’t taking the drug. So, building a sense of confidence in the approach that’s being taken to reduce apoB-containing lipoproteins is essential for long term successful management of risk.

**Dr. Grundy:** I agree with that.

**Dr. Brown:** What are the major unresolved issues? We’ve talked about several of them. Are there any others that you feel are important from your discussions with so many people from around the world? What do we need to address with new experimentation?

**Dr. Grundy:** Well, 1 of the problems that we see in the lipid clinic is a very high rate of referral for statin intolerance. This was not addressed very effectively in these recent guidelines. Maybe it’s because we don’t have a good answer to that issue, but that is one of the major unresolved issues. Perhaps the PCSK9 drugs or other drugs in combination with low-dose statin can help with statin intolerance.

I know that in clinical trials there does not seem to be a lot of statin intolerance. That’s hard for me to understand. It makes me even wonder whether the patients and physicians are appropriately indicting statins for their symptoms. I guess the trials could be wrong. Maybe the way the trials are done, they don’t pick up side effects very well. Perhaps there’s too much distance between the ones that look at the data and the ones that are doing the trial.

We see the same old story over and over, and these patients are not educated to give that story. There is a lot of muscle weakness and muscle problems associated with statins, and we don’t have the solution to that yet.

**Dr. Brown:** There are many other disorders of muscle and joint that occur in the elderly that seem to be forgotten when people get put on statins and the statin tends to get blamed for these things when they appear, but they were present in the practices of medicine, before 1987 when statins were introduced.

**Dr. Grundy:** They certainly were. We just didn’t know what to blame it on then.

**Dr. Brown:** Exactly.

**Dr. Grundy:** No, we see that all the time. People have disc disease or arthritis or other kinds of problems that are not related to statins.

**Dr. Brown:** When asking large numbers of people about their experience with statins, about 30% of the patients who were placed on a statin claim to be statin intolerant. The most important issue has been muscle aches and pains, so it is a major problem affecting millions of people. This has worried clinicians for a long time. We continue to seek a general approach and reasonable solutions to this issue. So, I think you’re absolutely right it is an extremely important issue.

Are there any other points you’d like to make about your recommendations?

**Dr. Grundy:** We have suggested incorporating an approach that has not been in earlier guidelines; that is, to recommend the use of lifetime risk assessment. We have data from epidemiology that allow us to project a person’s chances throughout his or her life of developing cardiovascular disease. I think this gives perspective. So, if you calculate a person’s lifetime risk, you may either modify the treatment, but maybe even more importantly, approach the patient differently. If you project out their likelihood of developing cardiovascular disease later in their life, it often has more meaning to the patient in primary prevention.

**Dr. Brown:** That would seem to be very important in people who are younger than those in our large epidemiologic studies, like Framingham where men younger than age 40 years or women younger than 50 years have very low risk when you consider a 10-year time frame. But when you talk about a 30- or 40-year time frame, it suddenly takes on a different picture.

**Dr. Grundy:** It certainly does. If you just take an example of a smoker, a smoker at age 30 is not likely to get lung cancer or a heart attack by age 40. Some of them do, but not many. But if you project their lifetime risk, it is enormous, right?
Dr. Brown: Absolutely.
We are going to have a very hard time making great progress in primary prevention other than through lifestyle change because physicians seem unlikely to prescribe adequate statin therapy when they are not confident that the patient has occult atherosclerosis.

Dr. Grundy: Lifestyle intervention is the cornerstone of primary prevention.

Dr. Brown: Tuberculosis taught us the lesson that you must not wait until you have clinical end points or more dramatically stated, a clinical catastrophe with multiple pulmonary cavities or a collapsed lung. You have to find the disease very early and treat it before the first clinical signs.

Dr. Grundy: It works in both sides, early and late but where you apply it earlier, you don’t need such intensive treatment.

Dr. Brown: Yes, that’s right. We have been treating risk, but we haven’t been treating the disease. If we had safe and inexpensive methods of diagnosing occult disease in a primary care office, it could make therapy much more rationale. I believe this concept is worth a serious research effort.

Dr. Grundy: Right. I hope we’re moving in that direction.

Dr. Brown: On behalf of the readership of the Journal, I want to thank you for joining me today and providing the background and rationale for the new IAS’s Global Recommendations for the Management of Dyslipidemia. Your sharing of these with the rest of the world should greatly aid those groups who are trying to provide guidance in countries where there have been no guidelines and in those considering revision of existing guidelines.