MORE AGGRESSIVE TREATMENT

**Dr. Kwiterovich:** With the release of the new NCEP [National Cholesterol Education Program] guidelines, is it time to get more aggressive with combination therapy, particularly for the patient with coronary artery disease (CAD)?

**Dr. McKenney:** Regardless of new guidelines, it’s time to get more aggressive. So many of CHD [coronary heart disease] patients either aren’t being treated or are not being treated to goal, and it’s a lingering problem. This is certainly something that the new guidelines have addressed and have tried to emphasize as much as they possibly can.

The new guidelines more precisely identify high-risk patients who require aggressive treatment, and it’s likely that there will be more patients who will need aggressive treatment.

**Dr. Hunninghake:** I basically agree with what Dr. McKenney said. I think we need to try to get patients to reach their suggested targets. With the new guidelines, many more patients will need to maintain their LDLs [low-density lipoprotein levels] at less than 100 [mg/dL], but the highest-risk patients (CHD patients), or those with equivalent CHD risk, are the ones who are not achieving target LDL goals.

There are 2 approaches to treat patients to goal. One is to give higher doses of a statin, which many physicians and other healthcare professionals are reluctant to do. The other approach is to use more combination therapy. The best data I have seen suggest that not more than 30% of people with coronary disease have LDLs less than 100 [mg/dL].

I think that is an overestimation of how many people are at goal because the studies are usually done in the high-prescriber statin users, the more likely people for using drugs. In reality, I think fewer than 30% are reaching that goal.

**Dr. Jones:** The new NCEP guidelines continue to advocate an LDL of less than 100 mg/dL in all CHD patients. We have evidence that less than a third of CHD patients are below 100 mg/dL, and the major reason, I believe, is failure to use higher, more adequate doses of statins or failure to use more potent statins. Even if physicians use higher doses of a statin, CHD patients may not achieve an LDL of less than 100 mg/dL because of intolerance to the dose or rare
biochemical abnormalities, such as increased transaminases. Adding a nonstatin LDL-lowering medication, such as a bile acid resin, can provide an additional 10% to 20% reduction in LDL levels. This additional effect can result in greater LDL reductions than would occur with doubling or quadrupling the dose of a given statin.

**Aggressiveness of Therapy in Patients with Other Risk Factors**

**Dr. Kwiterovich:** What about the patient with diabetes?

**Dr. Hunninghake:** I think it has been pretty well disseminated at various meetings that there will be a CHD risk equivalent category, and diabetes certainly falls into that category. So the goal in a patient with diabetes will be less than 100 mg/dL. Many patients who have other risk factors or other conditions will probably need to have a goal of less than 100 mg/dL.

**Dr. Kwiterovich:** How about the patients with coronary disease or diabetes that have hypertension or other risk factors? We’re always thinking about lipids, but what about treating them for their other risk factors as well?

**Dr. Hunninghake:** I think we do have to manage their other risk factors, and we probably aren’t doing a very good job doing that. I think some of the recent data suggest that in management of hypertension, we’re getting poorer at that instead of better.

For example, few people who have had a stroke are getting lipid-lowering therapy than people who have coronary disease. We really need to focus on getting that group under control, too.

**Dr. Kwiterovich:** I think that’s an excellent point, because for atherosclerotic stroke, lipid-lowering agents can also decrease the risk of stroke.

**Dr. Zhao:** The clinical and angiographic research data from our group and others supports combination therapy. In the early 1990s, we first published the data from the FATS [Familial Atherosclerosis Treatment Study] trial to show that combination therapy really can achieve atherothrombotic regression and further reduce clinical events. At last November’s American Heart Association meeting, Dr. Greg Brown reported the results on our HDL Atherosclerosis Treatment Study [HATS]. The combination of simvastatin and niacin reduced major clinical events by 60% to 90% (in CAD patients with low HDL [high-density lipoprotein]). The event reduction in HATS certainly has exceeded expectations for statins alone. We have put all the angiographic trials together and have found that conventional monotherapy results in a 35% reduction in clinical events: CAD death, non-fatal MI [myocardial infarction], recanalization procedures. With combination therapy, we see about a 50% reduction, on average.

**Combination Therapy: Best Bets**

**Dr. Hunninghake:** Dr. Zhao, you mentioned the diabetic patient, which brings up the metabolic syndrome or syndrome X. These patients often have mixed hyperlipidemia, with high triglycerides and low HDL. We also use statins in combination with the omega-3 fatty acids or fibrates when we need to get some additional lowering of triglycerides.

**Dr. Jones:** I agree. The most studied and safest combination is a statin plus a bile acid sequestrant. The possibility of drug-drug interaction is very rare, unlike combining a statin plus niacin or a statin plus fibrates. This might be able to see more patients on colestevalam with LDL below 100 mg/dL because of the improvement in compliance.

**Dr. Kowiterovich:** What about the patient who has both elevated triglycerides and cholesterol? The new NCEP guidelines suggest that the patient first be treated to his or her LDL goal. Then, if triglycerides remain above 200 mg/dL after the LDL goal has been achieved, the guidelines recommend that patients be treated to a second goal defined by non-HDL, which is set at 30 mg/dL above the patient’s LDL goal. To treat patients to the second goal, one could accentuate the LDL-lowering regimen as I mentioned earlier, or add niacin or a fibrate to the LDL-lowering regimen.

**Dr. Hunninghake:** If a person has really high triglycerides and the cholesterol is very low, or the LDL is very low, then I do feel that we are justified in initiating therapy with something like a fibrate, and then fine-tune it with LDL lowering.

**Dr. Jones:** There is one thing that we don’t know: all the data show that a lower LDL reduces risk, but we really don’t have conclusive data. What we lack showing that if triglycerides are then lowered or all these particles are altered, an additional reduction of risk is seen.

**Statins as First-Line Therapy**

**Dr. Kowiterovich:** The statins by themselves reduce risk about 30% to 40%, so there are still a lot of things we don’t understand about reducing risk. I think we need to consider trying to optimize the lipid profile. This leads to another question: should statins always be the first-line therapy now?

**Dr. Zhao:** No matter what combination we use, we will always consider a statin as a major component. The statin trials have produced the largest body of information about reduction of mortality and morbidity, in both the primary and secondary prevention settings. I still believe statins should be considered first for coronary disease patients and for the cardiovascular risk of the patient.

**As we reported at the American Heart Association meeting a couple of years ago, we offered a triple-therapy approach: lovastatin, reduced-dose niacin, and colestipol. We followed those patients, compared to others who went back to their own physicians for usual care. That comparison showed a fairly statistically significant difference in terms of survival and event-free (CAD death and non-fatal MI) survival.**

The good thing about combination therapy is that you can offer patients reduced doses. They don’t have to take a very high dose of niacin, so most of the people could tolerate it better. I think colestipol will really improve compliance. We might be able to see more patients on colestevalam with LDL below 100 mg/dL because of the improvement in compliance.

**Xue-Qiao Zhao, MD**
lar disease population. However, certain patients cannot tolerate a statin or LDL does not reach target on a statin. What should we do about them?

Dr. McKenney: I have 2 possible suggestions. If the person really needs a significant reduction in LDL, I will do my best to persuade that patient to try another statin. Some patients are never going to get to target unless they take a statin in combination with something else.

If a patient doesn’t need such a significant reduction in LDL, then other options are available. A true allergic reaction to a statin is very rare; in those cases, a drug such as clofibrate or one of the other sequestrants could be used. Then I would try to add something like niacin.

To get back to the original question, I think there is one situation where statins should not be first-line therapy, and that involves people who have significant chylomicronemia. Generally, if triglycerides rise above 750 mg/dL, the patient probably has chylomicronemia. I would use something like a fibrate or omega-3 fatty acids, especially in low-risk individuals who may not need dramatic LDL lowering.

Dr. McKenney: The biggest mistake I see with lipid-lowering therapy is the use of a statin to treat primary hypertriglyceridemia. That’s not the right choice. A fibrate or niacin would be preferred in these patients.

Dr. Kwiterovich: A lot of evidence indicates that the statins stabilize unstable plaques in the coronary arteries. There is some evidence that statins perhaps induce nitric oxide in the endothelial cells in the blood vessels of the brain, and that might be important in the prevention of stroke. Do niacin and fibric acid derivatives stabilize unstable plaques?

Dr. Hunninghake: I do not believe that all of the benefits with statins are simply due to plaque stabilization. I think there may be some kind of anti-inflammatory effect. I think the statins also probably have an antithrombotic effect. We really haven't tested for these effects with niacin or fibrates.

Dr. Kwiterovich: What about the patient who has coronary disease with a low HDL of 25 or 30 [mg/dL], and an LDL that is 90 or 100 [mg/dL]? Would you use a statin as a first-line drug in that kind of patient?

Dr. McKenney: I think we really have 2 choices. That patient can be treated with either a statin or gemfibrozil. On the basis of the VA-HIT [Veterans Affairs HDL Intervention] Trial, I don’t think we can say all fibrates, but maybe we have to limit it to gemfibrozil for now.

Dr. Kwiterovich: For isolated low HDL wouldn’t you consider nicin?

Dr. McKenney: I think you could add niacin, but we don’t have very much data that it decreases risk. I think the bigger question is whether we should use combination therapy in that group to both lower LDL and raise HDL. I probably would consider giving niacin to increase HDL.

Dr. Kwiterovich: Is particle size an issue when we discuss the different classes of drugs?

Dr. Jones: LDL particle size is important, since smaller denser particles appear to be more atherogenic than larger forms of LDL. Many patients with small, dense LDL have triglycerides exceeding 150 mg/dL, and HDL of less than 40 mg/dL, and they may have the cardiovascular metabolic syndrome. The drugs that lower triglycerides and increase HDL, such as fibrates and niacin, are most likely to improve LDL particle size. Statins have little or no effect on LDL particle size; they do, however, significantly reduce the numbers of smaller LDL particles, which is beneficial. Combining niacin or a fibrate with a statin would accomplish both a decrease in LDL particle number and increase LDL particle size. The same could be said for combining niacin or a fibrate with a bile acid inhibitor.

Dr. McKenney: Before we get carried away with fancy laboratory testing in our patients, we need to keep in mind that LDL is the main target of treatment and that the goal recommended by the NCEP should be sought. Having said that, the size of a statin, and probably a bile acid-resin-statin combination, to reach the LDL goal will also help correct the small dense LDL problem. There are publications, I with simvastatin, I with fluvastatin and I recently published with atorvastatin, which indicate that these drugs preferentially reduce small dense LDL particles in patients with atherogenic dyslipidemia characterized by high triglycerides and low HDL.

Dr. Hunninghake: You have raised another important issue. If you have achieved control of LDL, but you know the person has small dense LDL, you have to ask whether the person has gotten the maximum benefit. What kind of additional justification would we need to make the decision? Some physicians and the clinical significance of using these particles is still debatable. I think the 2 big players in the future will be apolipoprotein B (apoB) and non-HDL cholesterol levels. A true allergic reaction to a statin is very rare; in those cases, a drug such as colesevelam or some of the other sequestrants could be used. Then I would try to add something like niacin.

Dr. Kwiterovich: Before we get carried away with fancy laboratory testing in our patients, we need to keep in mind that LDL is the main target of treatment and that the goal recommended by the NCEP should be sought. Having said that, the size of a statin, and probably a bile acid-resin-statin combination, to reach the LDL goal will also help correct the small dense LDL problem. There are publications, I with simvastatin, I with fluvastatin and I recently published with atorvastatin, which indicate that these drugs preferentially reduce small dense LDL particles in patients with atherogenic dyslipidemia characterized by high triglycerides and low HDL.

COMBINATION THERAPY WITH STATINS

Dr. Kwiterovich: It’s certainly true that statins lower the total number of small, dense LDL particles, and they do it very effectively. However, have you achieved the maximal effect with a statin alone? Are there still too many residual small dense LDL particles? Combination therapy not only decreases the total number of small, dense LDL particles, but converts small dense particles into the larger, more buoyant particles.

Dr. McKenney: A combination that included niacin or a fibrate would have those effects, but I’m not sure about a combination with a bile acid resin.

Dr. Kwiterovich: Some data indicate that colesevelam might have the effect. Additionally, Dr. Greg Brown’s group at the University of Washington has done some work showing that a bile acid sequestrant, in combination with a statin, seem to increase the buoyancy of the LDL particles. As somebody who has worked with small, dense LDL for a while, it’s exciting to me to see that we can not only lower the total number of particles, but also change their buoyancy. I think that’s one of the great benefits of combination therapy.

TREATING TO MAXIMUM BENEFIT

Dr. Hunninghake: You have raised another important issue. If you have achieved control of LDL, but you know the person has small dense LDL, you have to ask whether the person has gotten the maximum benefit. What kind of additional justification would the person need to make the decision? Should it be some quantification of the lipoprotein particle number? Interpretations of the results are difficult for many physicians and the clinical significance of using these particles is still debatable.

I think the 2 big players in the future will be apolipoprotein B (apoB) and non-HDL cholesterol levels. A true allergic reaction to a statin is very rare; in those cases, a drug such as colesevelam or some of the other sequestrants could be used. Then I would try to add something like niacin.
patients whose CHD risk was high enough to make the use of drugs cost effective.

Dr. Hunninghake: That's really true. It's amazing how just minor changes in the recommendations can add another 5 to 10 million people to the drug therapy category, and that's difficult to justify.

Dr. McKenney: I know the Europeans have defined the primary prevention patients who are candidates for drug treatment as those with a 20% or more risk of a CHD event in the next 10 years. The recent US guidelines recognize these patients as CHD risk equivalents and recommend aggressive LDL-lowering treatment to a goal of less than 100 mg/dL. Our guidelines also recommend treatment of primary prevention patients who have less than a 20% 10-year risk, but set the treatment goal higher and try to guide the use of drugs to those with higher risk. What is your feeling on this?

Dr. Hunninghake: Just about every country in the world, except the United States, uses such percentages. Most of these countries use only 1 target number for therapy. In the United States, we have never been comfortable with that; we prefer 2 or 3 levels of risk. To get back to your question, I think there is no doubt that the group with > 20% 10-year risk should be treated aggressively. The questions now are should patients with 10-year risk receive drug therapy and what goals should be pursued?

The other big issue is whether only the 10-year risk should be considered, or if lifetime risk should be incorporated. One of the problems with absolute risk is that over the short term, the risk in women is generally much lower than in men, resulting in a number of gender controversies and nontreatment of many women.

Dr. Kwiterovich: The NCEP panel has always recommended being very conservative in treating women before menopause. I think gender should definitely be considered.

High Density Lipoprotein Effect on Cardiovacular Risk

Dr. Kwiterovich: We haven't commented on HDL particle size. It has been postulated that larger HDL particles presumably have a negative association with cardiovascular disease, whereas smaller HDL particles have a positive association with disease.

Dr. Hunninghake: I don’t totally understand that, but I believe that the observation is valid. When somebody comes into my office now with an HDL of 70 mg/dL, or some high number like that, I don't automatically assume that that is protected. I think we have to focus more on making sure we at least get the LDL under control. I have 8 people in my clinic who have HDLs over 80 mg/dL who have the most extensive vascular disease you could ever imagine. They basically fall into the category you're talking about.

Dr. Hunninghake: The basic problem with HDL is that it is viewed from an anatomical perspective, such as whether it's HDL-2 or HDL-3. We really need better functional measures to understand this process.

Treating Multiple Dyslipidemias

Dr. Kwiterovich: Are there any other parameters we would like to consider when treating patients with various risk factors? We haven't spent much time discussing the type of situation where LDL is successfully reduced but HDL is still low and the triglycerides are still high. At that point would you then try to increase HDL and lower triglycerides in that patient? Let's say the patient has coronary disease or diabetes.

Dr. Hunninghake: I think trying to increase HDL is good. The problem is that we don't have data that allows us to say what target we should be trying to achieve for HDL. I think there probably is a little bit more sentiment for thinking about triglycerides in that situation, even in the patient with low HDL. We come back to what we've already discussed: Is there a laboratory test that can indicate whether HDL or the triglycerides need to be altered? If you have LDL of 200 mg/dL, or the apoB 100. Non-HDL cholesterol will be recommended as a secondary target for patients with triglycerides greater than 200 mg/dL in the future.

Dr. Jone: In some patients with elevated lipoprotein(a) (Lp(a)), niacin can lower this particle. It is also important to lower LDL-C levels in patients with high Lp(a), greater than 25 mg/dL. The patient with high LDL and high Lp(a) would do well with a statin plus niacin, or resin plus niacin, or with 3 drugs—a statin, a resin, and niacin.

Titratting the Statin Dose

Dr. Kwiterovich: Should physicians always titrate a statin dose 2 or 3 times before adding another agent?

Dr. McKenney: The word "always" tells you immediately you can say no and be right. No, they should always be titrated 2 or 3 times. I hope we’re moving more toward a blurring of what is a starting dose of a statin and thinking more about where we want to end up. We may not need to be titrating so much, but, first of all, simply selecting the dose that we think is most appropriate to achieve the goal in that patient.

Second, I think selecting the treatment regimen up front to get to your goal makes sense, and that might actually be a combination. You may not be able to titrate enough to get to your goal. If you can see every front if you understand, at the beginning, then you don’t have to go through all of these costly and bothersome steps. Think prospectively of where you are, where you need to go, and what is the best path to get you there.

Dr. Zhao: I agree.

Dr. Hunninghake: That’s really a major problem, though, right now, because most of the data depends on how you define the starting dose of the statin. I think most of the data suggest that about 65% to 75% of the people never go beyond the starting dose of the statin. Therefore, you will frequently not achieve target goals, especially in higher-risk patients.

What, now what I say now may not be quite right according to the official prescribing information. You see somebody comes in with a LDL of 240 mg/dL. It doesn't make sense to start him on or lower the starting dose of, what you know that person is going to need more, and it just costs a lot to keep titrating. I think we're also still afraid of high-dose statins. The data from all the trials show that you get elevated transaminase levels in only a small percentage of patients, particularly even with high doses of statins. Also, there are many patients in the current clinical trials who have LDL levels below 50 mg/dL, and there is no evidence of any kind of adverse effect from the low LDL. We don't have to be afraid to give the higher dose. Someday I hope we start with higher doses and then back titrate if we have exceeded the target reduction in LDL levels.

Dr. Jone: In every dose titration of a statin results in 6% to 7% additional lowering of LDL, and this should be considered as a physician tries to achieve any given LDL goal. Titrating a statin upward through 2 or 3 doses may provide only an additional 15% to 20% LDL reduction. An alternative would be to add a synergistic agent that will produce an additional 15% to 20% LDL reduction. This can be accomplished by adding a bile acid resin.

Dr. Kwiterovich: We do have the genetic model, hypo-beta-lipoproteinemia, which affects about 1 in 10,000 people. Those patients have HDL cholesterol levels of 50 or 60 mg/dL.

These patients have a truncated apoB 100, and the low LDL-C is actually associated with longevity.

Dr. Hunninghake: We actually published a paper a number of years ago, from one of our titrate-to-dose studies, showing a significant increase in cost by needing to titrate the people, at least in the first year.

In this study we started at the lowest dose statin and then titrated to goal.

Dr. Zhao: Yes, I think that's still the practice. People are still worried about the safety of a high-dose statin. Many practitioners always select a low dose, then titrate upward.

Dr. Kwiterovich: A lot of patients with coronary disease don't have exceptionally high LDL cholesterol, so if the proper dose of a statin is selected, the LDL is reduced to goal.

Peter O. Kwiterovich, Jr., MD

Discussion Point

“A lot of patients with coronary disease don’t have exceptionally high LDL cholesterol, so if the proper dose of a statin is selected, the LDL is reduced to goal.”
TREATING YOUNGER PATIENTS AT HIGH RISK

Dr. Kwiterovich: Should nonsystemic therapy be considered for younger patients now that tolerable agents are available?

Dr. McKenney: If we pick up on Dr. Hunninghake’s point earlier about using a 10-year risk assessment, we might identify women who would qualify for treatment. We may also consider the use of lifetime risk to guide our decisions. For example, if you had a female patient with a very high LDL level and a strong family history but few risk factors, you might find the 10-year risk to be low but the lifetime risk would be high. In fact, this patient could have familial hypercholesterolemia. I think most of us would consider drug treatment in this patient if lifestyle modification was not sufficient to achieve the treatment goal alone.

Dr. Kwiterovich: I agree. This might be appropriate in families with familial hypercholesterolemia being the real problem, involving patients in their 20s or even younger, for example, and a parent had bypass surgery at 32. I can’t predict whether the patient is going to be like the parent, in which case I certainly would treat.

That’s the problem with very high-risk young people; a precise prediction of what is going to happen to them can’t be made. In these situations, the choices are to do nothing, which would be not to treat with a medication, or to treat with a medication that is likely to do some good, unlikely to do harm. I sort of favor treating under those circumstances.

Dr. McKenney: The family history probably guides you.

Dr. Kwiterovich: Definitely.

Dr. Hunninghake: Another factor is beginning to play a role in these situations, and that is cost effectiveness. I think all current guidelines are based upon cost effectiveness. With high-risk younger people, we are unsure about the best approach for them. One thing that has really grabbed my attention in the last couple of years is some work that Steve Nissen has done in the heart transplant program at the Cleveland Clinic. He has evaluated the donor hearts from people selected because they are supposed to have good hearts. Of the 20-year-olds, more than 20% have huge atheromas. Of the 30-year-olds, the figure is 30%. These are people who would actually have benefited from lipid-lowering therapy, but it would take a number of years before they get to the vulnerable plaque. Sometimes you don’t get a second chance to treat a vulnerable plaque. The first clinical event is the first opportunity for treatment.

Dr. Kwiterovich: I think that’s an excellent point; making us realize that we need better diagnostic methods or noninvasive methods to identify those people that have such lesions very early.

Dr. Zhao: What about adding electron beam computed tomography (EBCT) to the workup? The EBCT calcium score appears to provide additive information to predict a person’s future risk. Is that something that should be considered?

Dr. Hunninghake: The problem with ‘making official recommendations like that, whether it’s doing carotid ultrasound or EBCT or whatever’, is that, sadly, everybody in the population gets these tests, and that costs an enormous amount. Now everybody is interested in C-reactive protein, but I personally think we’re not ready to put that in prime time yet. I think it’s a good predictor for a population, but I don’t think we know enough in an individual patient to be able to interpret the results. What we really need is the ability to identify the person who has the earliest manifestations of vascular disease and then start treating that person.

Dr. Kwiterovich: What about the issue of nonsystemic therapy for younger patients, now that tolerable agents are available? Some people feel that colesevelam could be quite useful. If the patient were male, you could use a statin.

Dr. Jones: Nonsystemic lipid-lowering therapy is a good option for younger men and for women of childbearing age. It is also an option for children and adolescents with a heterozygous familial hypercholesterolemia.

Dr. Hunninghake: I think for women of childbearing potential, we probably still would go with a nonsystemic therapy. I think the data for long-term safety of statins is good. I don’t have any concerns about using it in young males.

Dr. Kwiterovich: You wouldn’t want to give a statin to a 35-year-old who wants to conceive because she might get pregnant while she is taking the statin?

Dr. McKenney: Another possibility is that the statin is having a teratogenic effect. We have treated people over 7 years, 8 years, 10 years, and we have not seen that.

Dr. Hunninghake: Right.

Dr. Zhao: I think there was an article published about loss of efficacy in LDL lowering with long-term use of atorvastatin. We have treated people over 7 years, 8 years, 10 years, and we have not seen that.

Dr. McKenney: Another possibility is that the patient is not following the diet. People start out highly motivated to stay on a diet low in cholesterol and saturated fat, and then they go off the diet. This will compromise the effectiveness of the statins.

Dr. Zhao: Right.

Dr. Hunninghake: Yes, I think those are the main things. Once in a blue moon something else has happened to these people. They developed hypocholesterolemia, or something like that.

Dr. Zhao: A young patient who joined our study said she had no plans to get pregnant or have a family, and then a year into the study of a statin trial, she changed her mind. I just had to drop her out. Becoming pregnant while on a statin is too dangerous.

TREATING MYOCARDIAL INFARCTION PATIENTS

Dr. Kwiterovich: Another issue we might want to consider is the evidence that if you treat a person with a statin after a myocardial infarction, starting before they leave the hospital, they live longer.

Dr. Zhao: At the American College of Cardiology this year, a new meta-analysis was done on trials of antiplatelet therapy in acute coronary syndromes. The analysis showed that lipid-lowering therapy was associated, independently from antiplatelet therapy, with a lower event rate at follow-up.

Dr. Hunninghake: Another issue is that if people are started on therapy before they go home from the hospital, they are more likely to be on statins 1 and 2 years later.

Dr. Zhao: We’ve discussed the most commonly asked questions regarding primary and secondary presentations of cardiovascular disease. We have similar concerns about loss of efficacy in LDL lowering with long-term use of atorvastatin. We have treated people over 7 years, 8 years, 10 years, and we have not seen that.

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