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"Hot Summer" Controversies

This *Heartbeat* will comment on two provocative and controversial issues that have topped the medical headlines this summer. Interestingly, each revolves around a less than optimal, highly complex statistical meta-analysis of dozens of studies. The first is the increased cardiovascular (CV) risk of Avandia and the second is associated cancer risk with aggressive statin therapy.

The variety of interpretations based on the same inconclusive data is amazing. Everyone agrees upon the "clear cut" data, but frequently there are areas of dispute among the experts. Accordingly, our job is to recognize these varying opinions and use our best judgment in treating our patients. Like so many other things in medicine, clinical interpretation is the key to proper patient care. This *Heartbeat* will try to give you a read on that bottom line.

Rosiglitazone Controversy

Nissen and Wolski's meta-analysis of possible CV risk of rosiglitazone therapy has reverberated from the clinician's office and cardiology journal club to the halls of Congress. Despite many limitations of the data which was used, the authors state that review suggests a statistically significant CV risk associated with the use of rosiglitazone (Avandia) and call for more robust studies of the drug's CV risks and an evaluation of source data from GlaxoSmithKline (GSK) and the FDA.[1] The authors also suggest that providers and patients should weigh the possible CV risks of rosiglitazone when considering possible therapies in the management of type 2 Diabetes (T2DM).

Because of these concerns, an unscheduled interim analysis from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD)—a multi-center, drug-company-sponsored, open-label, noninferiority trial—was performed in hopes of quelling the controversy.[2] Unfortunately, the data were inconclusive with regard to the overall risk of hospitalization or cardiovascular-related deaths with rosiglitazone, although there was a clear association between rosiglitazone and congestive heart failure. Furthermore, the data were not robust enough to determine whether rosiglitazone is linked to an increased risk of myocardial infarction (MI). Rosiglitazone cardiotoxicity was not excluded.

Caution Urged on Rosiglitazone Use

But what does the controversy mean for physicians and their patients with T2DM? A new Cochrane review of rosiglitazone,—released online July 18th—has found no evidence of any benefits of the drug over other diabetes medications and, because of side effects such as edema, fractures, and possible increased risk of MI, the review advises a "very cautious approach

to rosiglitazone use" and recommends other antidiabetic medications be used if possible.[3]
The study concludes that the benefit/risk ratio of rosiglitazone therapy in T2DM needs urgent clarification and that patient-oriented, end-point studies are urgently needed for the management of T2DM. But they add that it appears questionable whether new studies with rosiglitazone would be ethical, given the fact that less dangerous therapeutic alternatives exist.

Older and Cheaper Better than New…especially if increased risk

A systematic review comparing newer vs. older drug treatments of T2DM showed that older agents have similar effects on glycemic control, according to an article published online in the July 16 Early Release Articles issue and to appear in the September 18 print issue of the *Annals of Internal Medicine*.[4]

"Compared with newer, more expensive agents [thiazolidinediones (Avandia, Actos), α-glucosidase inhibitors (Acarbose), and meglitinides (Prandin, Starlix)], older significantly cheaper agents (second-generation sulfonylureas and metformin) have similar or superior effects on glycemic control (~ 1% decrease on Hg A-1C) and other cardiovascular risk factors (blood pressure, lipid levels, and body weight)," the authors conclude. "Each oral diabetes agent is associated with adverse events that counterbalance its benefits." Overall, metformin seemed to have the best profile of benefit to risk and cost (equal or better Hg A-1C lowering, lowering of low density cholesterol (LDL-C), weight neutrality and no associated hypoglycemia—supporting its number one recommendation per recent American Diabetic Association Guidelines. Importantly, patients without comorbid conditions who were treated with metformin were no more likely to develop lactic acidosis than were those treated with other oral diabetes agents.

Large, long-term comparative studies on major clinical end points such as MI, chronic kidney disease, and CV mortality are needed to determine definitively the comparative effects of the oral diabetes agents, especially in light of recent controversy regarding rosiglitazone.

This review also seems to support caution regarding use of rosiglitazone using it as a 3rd or 4th line agent at best. There doesn't seem to be any reason to use an agent which *may be* associated with increased CV risk in high-risk T2DM patients which is more expensive and isn't proven any better. We have a lot of choices for oral hypoglycemic agents. For those T2DM patients without HF who are on rosiglitazone, switching to the pioglitazone (Actos) would seem prudent.

Separate from this argument, the evidence is overwhelming that Avandia and Actos worsen heart failure. Both available glitazones should be used with caution in all heart failure (HF) patients—especially Class III or IV.

Avandia Backed but With Warnings

A federal drug advisory panel, after reviewing the data and having considerable debate, voted overwhelmingly on Monday July 31 to recommend that Avandia remain on the market, even after finding that it raised the risks of heart attacks. The panel's recommendations are not binding, but the FDA usually follows them.

Most panelists who voted in favor of keeping Avandia on the market suggested a variety of labeling changes including a "black box" warning about its effect on MI risk and new "contraindications" stating it should not be used in high-risk patients such as those with known coronary artery disease (CAD) or those who have been long term users of insulin.

Statin Safety Controversy

A new provocative meta-analysis, initially designed to determine if there was a correlation between the extent to which statins lowered LDL-C and liver and muscle toxicity, suggests that the cardiovascular benefits of achieved

levels of LDL cholesterol might be offset by an increased risk of cancer.[5] In an analysis of patients enrolled in large, randomized statin trials, investigators observed a "significant and linear relationship" between achieved LDL levels and the risk of new cancer cases.

"The statin trials have clearly shown that statin therapy, overall, reduces cardiovascular risk," said senior investigator **Dr Richard Karas** (Tufts-New England Medical Center, Boston, MA). "These findings don't change that. They're based on the same studies. But a component of that, perhaps one of the costs of that, is a relationship between the LDL lowering and cancer risk."

Karas also said there is concern about how the new findings will be reported and interpreted, especially if the message causes some patients to stop taking statins. "What we're always doing in terms of trying to take care of patients is balance benefit and risk," he said. "This analysis was really focused on trying to enhance our understanding of the risk side of that equation. It has produced a provocative and interesting result that raises a lot of new questions... but it's a complicated message, and the conclusion people will jump to if they are not being careful is that statins cause cancer. We don't know that, and our data don't show that."

The conclusion from two accompanying editorials is that "until additional data are available, adherence to existing National Cholesterol Education Program guidelines is appropriate[6], especially with regard to the recommendation that lower LDL-C goals to approximately 70 mg/dl **apply only** to high-risk patients."[7] [8] High-risk patients, in whom this optional 70mg/dL LDL-C should be applied, are those with acute coronary syndrome, recent stroke or TIA or those with known CAD and additional risk such as T2DM or metabolic syndrome, tobacco dependence disorder, uncontrolled hypertension or recurrent symptomatology.

Until we have better answers it may be prudent to use combination therapies to get to optional more aggressive LDL-C and non-HDL-C goals instead of mega-dose statins. Applying the philosophy of "*the lower dose of 2 or 3 meds is safer than the high dose of one drug"* may be a safer alternative in case the cancer association is related to statin dose rather than low LDL-C itself or to cancer's causation of lower LDL-C or some combination of these factors.

"You can't be too rich or too thin or have too low a cholesterol level".

According to the results of another new study, statins used in patients with extremely low LDL cholesterol levels are safe and may lead to improved survival.[9] This was observed across multiple subgroups, including patients with LDL cholesterol levels <40 mg/dL and those without documented CAD.

"We're seeing more and more people coming back to clinic with cholesterol levels well below the goal we had intended," said lead investigator **Dr Nicholas Leeper** (Stanford University School of Medicine, CA). "If you start a patient after his acute coronary syndrome on a statin, and he comes back a few months later and his LDL is 50 mg/dL, or even 40 mg/dL, we were realizing that we didn't know what to do with these patients, whether it was safe to continue, whether we had to back off or stop treatment. We also didn't know what happens to patients who come in with very low LDL levels, for whatever reason, if they are to be started with a statin."

This study showed not only that the drugs are safe, with *no risk of cancer at two years*, but they also might improve survival in patients with very low LDL cholesterol levels.

As to potential side effects, statin therapy was not associated with an increase in any adverse events. No cases of rhabdomyolysis were reported, nor was there a risk of developing liver enzyme elevations. Importantly, there was no

increase in the risk of malignancy or renal insufficiency in 60% of the 6000 identified patients with LDL cholesterol levels <60 mg/dL. Patients were, on average, 65 years old, and approximately half had diabetes mellitus or ischemic heart disease.

These results seem reassuring, but we should question whether a 2 year study is long enough to conclude that statins have no *long-term* risk.

More study is needed.

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