Above and Beyond

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Beyond glucose and LDL-C

For some time, data has supported the aggressive lowering of glucose and LDL-C in diabetic patients with an extremely high risk of coronary events. This *Heartbeat* will review recent studies that support the premise that even more can be done. In addition to lowering LDL-C further, Glitazones, aimed at lowering serum glucose and Hemoglobin A1c (HgA1c), and fenofibrates, aimed at increasing HDL-C and lowering triglycerides (TG), can also further decrease the risk of cardiovascular (CV) events in high-risk diabetic patients.

IDEAL LDL-C

More data has become available supporting the premise for LDL-C that *lower is better* for preventing MI, stroke, the need for cardiac procedures and death. On the basis of the IDEAL[1] and TNT[2] studies superimposed on PROVE-IT[3], we can reasonably assume that the next update of NCEP Guidelines will push goal LDL-C to < 100mg/dL in people at risk and to < 70mg/dL in anyone with known vascular disease. These goals can be attained with statins or a statin/ezetimibe combination. But more still has to be done beyond statins. Intensive statin treatment does not prevent CV events in all patients. There is always room for improvement, and combinations of medications on top of statins will move us closer.

Coke vs Pepsi? (Glitazones)

In a study presented at the 2005 American Heart Association meetings in November, pioglitazone (Actos) and rosiglitazone (Avandia), two, peroxisome proliferator-activated receptor-γ (PPAR-γ) antagonist insulin sensitizing drugs, are compared in patients with Type 2 diabetes (T2DM) and dyslipidemia.[4] Pioglitazone demonstrated significant improvements in TG (decreased), HDL-C (increased), non-HDL-C (decreased), and LDL size (increased) particle concentration (decreased) compared to rosiglitazone. Both agents improved blood sugar control and HgA1c, and increased LDL-C. Effects on cardio C-reactive protein (CRP), insulin levels and free fatty acids were equal.

Whether the differences between the two glitazones convert to improved CV outcomes is not yet known, but another study attempts to answer part of this question. The authors of the **PRO**spective Piogli**A**zone **C**linical **T**rial **I**n macro**V**ascular **E**vents (**PROactive trial**), in a subgroup analysis, concluded that pioglitazone reduces the composite endpoint of all-cause mortality, non fatal MI and stroke in patients with T2DM by 16%.[5] It also reduced the risk of acute coronary syndrome (ACS). There was an insignificant 10% lowering of the study's primary endpoint of all macrovascular events versus placebo. The pioglitazone-treated group had a better metabolic profile in terms of glucose, HDL-C and TG concentrations, and better blood pressures at the end of the study

than at the beginning, which could help explain the improved CV outcomes.

PROactive Provoking Discussion (1) Overall safety and tolerability were good, but there was a non-significant trend for more edema and HF admissions in the pioglitazone group (deaths were not increased). This needs more study. (2) Letters to the editor take issue with the fact that the conclusions are based primarily on the secondary endpoint, while the primary endpoint was globally negative. Others point out that the lower blood pressure was more than enough to explain the whole potential CV benefit of pioglitazone.

Conclusion: This PROactive study is *hypothesis generating*—not *ground breaking*—proof, but suggests further CV benefit in addition to reducing need for insulin by using pioglitazone in T2DM. Pioglitazone is the first diabetic drug that has shown evidence-based results to decrease mortality, MI and ACS. It is reasonable to suggest that a glitazone be considered as initial therapy in appropriate T2DM patients to further decrease CV risk and blood sugars along with aspirin, statins and angiotensin II blockade.

Fenofibrates

While the PROactive trial attempts to answer questions of whether pioglitazone reduces CV morbidity and mortality in patients with T2DM, and whether it's safe, the **F**enofibrate **I**ntervention and **E**vent **L**owering in **D**iabetes (**FIELD**) study attempts to answer the same questions regarding fenofibrates in T2DM.[6] Again, analogous to the PROactive study with pioglitazone, there were mixed results with fenofibrate in the FIELD study in diabetics. It failed to significantly reduce the primary end point in overall coronary events: coronary heart disease (CHD) death or non-fatal MI (an insignificant 11% decrease). The FIELD study did significantly decrease the non-fatal MI component by 24%. A major finding of the study was that fenofibrate also decreased microvascular events. There was a significant 21% lower relative risk of needing revascularization, a slower progression of albuminuria, and a lower rate of laser treatment for diabetic retinopathy.

Concerns: A non-significant increase in CHD deaths, most likely secondary to chance. There were no complications of statin + fenofibrates in about 300 patients, supporting the safety of the combination.

Conclusions: "Close, but no cigar." It seems that patients aren't dying like they used to, and the placebo groups in recent studies do too well. The event rates are significantly decreased in the placebo groups. This is because of much better baseline treatment. Specifically in FIELD, there was a much higher rate of starting statin therapy in the placebo group of T2DM patients, which might have masked a moderately larger treatment benefit of fenofibrate. The final lipid values showed minimal effects of fenofibrate, as doctors felt compelled to add statins after the results of Heart Prevention Study (HPS) became available.[7] Taking all this into consideration, fenofibrates should not be considered as a replacement for statins to decrease CV risk in T2DM. It does appear, though, that they offer further benefit in conjunction with statins and it would be reasonable to add a fenofibrate to a statin when non-HDL-C is high, HDL-C is low or TGs are high in these high-risk patients.

Discussion/Summary:

The evidence of the effectiveness of statins in the treatment of stable CHD continues to grow. Large-scale, randomized, secondary-prevention trials involving patients with CHD have shown that statins reduce the clinical consequences of atherosclerosis, including death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for unstable angina pectoris and heart failure, as well as the need for coronary revascularization. Current guidelines recommend a low-density lipoprotein (LDL) cholesterol level of less than 100 mg/dL as the goal for patients with stable CHD and a goal of

70 mg/dL be considered in high-risk CHD (ACS, DM, tobacco dependence etc). It is anticipated, based on recent studies, that these goals will be lowered to LDL-C of < 100mg/dl in those at risk (primary prevention) and to < 70mg/dL in those with known CVD.

Although treatment with statins has reduced cholesterol levels and lowered CVD mortality rates approximately 30%, all the clinical studies have indicated that CV events continue to occur in the other 70%. Despite progress in the identification of risk factors and the development of highly effective clinical tools, deaths from CVD continue to rise worldwide. The obesity epidemic, metabolic syndrome and the rising incidence of T2DM in our young and aging baby boomers have led to an upsurge in CVD.

Additional approaches beyond statins have to be tried. The two studies discussed in this *Heartbeat* were generally positive (not as much as expected) and should alert physicians to the importance of CV morbidity in T2DM patients. Scott Grundy, Chairman of NCEP, states, "As it gets harder and harder to prove a benefit of new medicines, doctors will have to make due with mixed results more and more often." This is obviously due to numerous aggressive background beneficial treatments (statins, aspirin, A II blockade and beta-blockers. Just as in IDEAL (atorvastatin 80mg compared to simvastatin 40mg) benefits will be more incremental and not as dramatic (another study where the primary outcome wasn't proven but benefits are present with more aggressive therapy).

In PROactive, glitazones improved CV outcomes and delayed time to insulin therapy while controlling sugars and HgA1c. In FIELD, fenofibrates demonstrated improved macrovascular and microvascular outcomes. Both of these treatments should be considered in T2DM to decrease CV risk above and beyond that obtained with good glucose control and statins along with other indicated beneficial treatments including an appropriate diet and exercise program.

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Mario L Maiese DO, FACC, FACOI
Clinical Associate Professor of Medicine, UMDNJSOM Email: maiese1@comcast.net
Heartbeats online: www.sjhg.org.

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[7] Heart Protection Study (**HPS**) Collaborative Group. HPS of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomized, placebo controlled trial. Lancet 2002; 360: 7-22.