Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 15, NUMBER 5 PAGES 9-10 MAY 2010

Statins and risk of developing diabetes

Source: Sattar N, et al. Statins and risk of incident diabetes. *Lancet* 2010;375: 735-742.

THERE IS LITTLE DISPUTE REGARDING THE beneficial reduction in CV events seen with statin treatment of dyslipidemic patients. At the same time, however, conflicting evidence has suggested that statin treatment might be associated with an increased risk of new-onset diabetes.

Sattar et al performed a meta-analysis of data from large statin clinical trials (n = 13), totalling almost 100,000 patients. During a mean follow-up of 4 years, 9% more individuals developed new diabetes on a statin than patients not treated with a statin. Since CV risk reduction was still favorably influenced by statin treatment, this small increase incidence of diabetes was either not sufficient to offset other beneficial vascular effects, or, once diabetes developed, statin protection was already on board, or perhaps both factors were influential.

You may recall that in hypertension treatment trials, a similar problem has been identified. Chlorthalidone (ALLHAT) had a significantly greater risk for incidence of new diabetes than comparators, yet this adverse effect did not seem to adversely affect CV event rates.

The mechanism by which statins increase risk for diabetes is obscure. This data analysis calculated that 255 subjects would have to be treated with a statin for 4 years to incur 1 additional new case of diabetes. Fortunately, if the small increase is real, it is strongly counterbalanced by well-documented reductions in CV events.

Maximize benefits of metform in DM2

Source: Brown JB, et al. Secondary failure of metformin monotherapy in clinical practice. *Diabetes Care* 2010;33:501-506.

TO DATE, CONTROLLED TRIALS INDICATE THAT no matter what pharmacotherapy is used to control glucose in type 2 diabetes (DM2), one can anticpate a progressive loss of control over time. Loss of efficacy is termed secondary failure: An initially effective medication later becomes insufficient to maintain control. It seems to me that this is too harsh an indictment of pharmacotherapy, since even if the medication continues with similar action over long time periods, confounders such as weight gain, inherent disease progression, and addition of confounding comorbidities might make it appear as if the medication is failing, when in reality, counterbalancing forces are increasing.

In any case, Brown et al performed an observational cohort study of DM2 subjects (n = 1799) initially treated with metformin monotherapy successfully (i.e., able to maintain an A1c < 7.0 without adding a second agent). Secondary failure was defined as either the addition of a second agent, or an increase of A1c above 7.0 while still on monotherapy. Subjects who required additional therapy within the first 6 months of metformin treatment were regarded as primary failure, and were excluded from this analysis.

In subjects able to maintain good control with initial metformin monotherapy, secondary failure occurred at a rate of 17% per year. Predictors of higher failure rates included longer duration of diabetes before treatment and higher baseline A1c at initiation of treatment. These data suggest that early initiation of treatment, especially when A1c is not yet markedly elevated, results in greater durability of metformin efficacy.

Prediabetes therapy and beta-cell function

Source: Hanley AJ, et al. Effect of rosiglitazone and ramipril on {beta}-cell function in people with impaired glucose tolerance or impaired fasting glucose. *Diabetes Care* 2010;33:608-613.

PREDIABETES (PDM) IS DEFINED AS EITHER impaired fasting glucose (FBG = 100-125 mg/dL), impaired glucose tolerance (IGT; 2-hour post-load glucose = 140-199 mg/dL), or supranormal but not diabetic A1c (A1c = 5.7-6.4). Untreated pDM predictably progresses to frank DM at a rate of about 7%-10% per year. Numerous interventions have been shown to alter the progression from pDM to diabetes, including diet, exercise, metformin, acarbose, orlistat, and thiazolidinediones; this year, nateglinide, an insulin secretagogue, was not confirmed to delay progression from pDM to diabetes.

Hopefully, treatments to prevent diabetes will also impact beta-cell function favorably, rather than simply compensate for progressive metabolic decline. The DREAM trial (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) randomized 5269 pDM subjects to ramipril and/or rosigliatoze. A substudy of DREAM (n = 982) had measurements of beta-cell function at baseline and periodically during the 3-year (median) follow-up, as well as measurements of progression from pDM to DM.

Subjects randomized to ramipril did not experience any meaningful change

in beta-cell function. In contrast, rosiglitazone-treated subjects enjoyed substantial improvements in beta-cell function. Benefits were less in pDM subjects who only manifest IFG compared with IGT or both.

In addition to reducing beta cells induced by glucotoxicity, thiazolidinediones lower free fatty acid levels, which may favorably affect beta-cell apoptosis.

Onychomycosis: Long-term follow-up

Source: Piraccini BM, et al. Long-term follow-up of toenail onychomycosis caused by dermatophytes after successful treatment with systemic antifungal agents. *J Am Acad Dermatol* 2010;62:411-414.

Although onychomycosis (ONCM) is often considered a cosmetic problem, some patients suffer significant disability due to foot pain, and difficulty wearing shoes. The treatment course for toenail ONCM is lengthy and costly. There are few data on long-term follow-up to ascertain recurrence rates, although prevailing opinion suggests recurrence is common.

Praccini et al performed a prospective study of ONCM patients (n = 73) who had been treated with pulse therapy (treatment 1 week/month for 6 months) with terbinafine or itraconazole. After clinical cure, subjects were prospectively followed for 7 years. Cure was defined as normalized clinical appearance and negative fungus culture.

Clinical Briefs in Primary Care™ is published monthly by AHC Media LLC.

Associate Publisher: Coles McKagen. **Editor:** Stephen Brunton, MD. **Senior Managing Editor:** Paula Cousins. This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: paula.cousins@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media LLC 3525 Piedmont Road, Building Six, Suite 400 Atlanta, GA 30305.

AHC Media LLC

Patients were seen every 6 months during follow-up. Overall, recurrence developed in 16.4% of subjects. Each case of recurrence involved the same organism identified in the original infection. However, the recurrence rate for itraconazole was 3-fold greater than terbinafine. Terbinafine is widely regarded as the treatment of choice for toenail ONCM; this trial suggests superior durability of cure for terbinafine when compared with itraconazole.

Diagnostic yield of elective coronary angiography

Source: Patel MR, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;362:886-895.

Current recommendations suggest that in stable persons under consideration for CAD evaluation, low-risk individuals be observed, high-risk patients be triaged to coronary angiography, and intermediate-risk persons be further stratified by means of non-invasive testing. Such guidance is structured to minimize unnecessary invasive investigations in low-risk individuals, and to identify — in the group of intermediate risk — those who merit follow-up with angiography.

The American College of Cardiology National Cardiovascular Data Registry provided information on patients without known CAD (n = 398,978) who received coronary angiography (electively) at hospitals in the United States during a 4-year interval commencing January, 2004.

Obstructive CAD was defined as at least 50% stenosis of the left main coronary artery (or greater degrees of stenosis of epicardial vessels). Catheterization determined that slightly more than one-third of patients had obstructive CAD. In addition to the disappointingly low percentage of individuals identified with CAD on angiography, this study also provided insights about the concordance of risk and use of non-invasive testing (i.e., stress testing). When non-invasive testing had preceded angiography, subjects' baseline risk category was at odds with the current recommendations focusing upon refinement of risk in persons at intermediate Framingham scores, in that those with high Framingham risk scores were disproportionately represented. The authors suggest that the diagnostic yield based upon current practice needs improvement.

Thyroid hormone analogue for dyslipidemia

Source: Ladenson PW, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. *N Engl J Med* 2010;362:906-916.

The role of statins in treatment of dyslipidemia is well established. There are, however, limitations of statins: Residual risk is substantial, not all persons can tolerate statins, and, even with full-dose statin treatment, some patients do not achieve lipid goals.

The role of the thyroid in lipid metabolism has long been a matter of scientific interest. It is recommended that patients with dyslipidemia undergo thyroid function testing since hypothyroidism, although only present in a small percentage of dyslipidemic patients, is readily correctible and offers meaningful lipid improvements. Enhancement of thyroid activity has favorable lipid effects. As far back as the 1960s, investigators were curious enough about thyroid hormone and vascular disease to enroll men in the Coronary Drug Project (1965) and randomize them to d-thyroxine, which was felt at the time (mistakenly) to have essentially no effect on sympathetic nervous system sensitivity, but favorable effects on lipids.

Eprotirome (EPR) is an analogue of thyroid homone which has preferential affinity for thyroid receptors that modulate lipid lowering, as compared to cardiac receptors. A randomized placebo-controlled, double-blind study was done among patients on an NCEP step 1 diet and a statin (simvastatin or atorvastatin). Patients (n = 329) received statin plus either EPR or placebo for 12 weeks.

At the end of the trial, very favorable lipid effects were reported with the addition of EPR to a statin: a 22%-32% reduction in LDL, a 6- to 9-fold increase in patients achieving an LDL < 100 mg/dL, as well as favorable effects on triglycerides and apoB (all dose-dependent). A small reduction in HDL was seen. There was no change in heart rate or BP. Selective activation of thyroid receptors may one day provide an additional path for successful lipid modulation.