Clinical Briefs in Primary Care™

The essential monthly primary care update

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# Rosiglitazone and CV Risk

Home PD, et al. *N Engl J Med.* 2007;357:28-38.

The recent indication in an article by Nissen, et al (*N Engl J Med.* 2007;356:2457-2471) that rosiglitazone (ROSI) might actually increase cardiovascular (CV) risk was met with surprise and dismay by many clinicians and their patients alike. Even though subsequent commentary on the newly-identified risk profile suggested that such conclusions should be considered "preliminary," because CV disease is the predominant cause of death in diabetics—in disproportion to the general population—providers continue to experience consternation.

In an attempt to provide clarification, Home, et al provide data from the RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes), which although not yet completed, offers almost 4 years of follow-up on more than 4,000 diabetics.

In RECORD, subjects not achieving adequate control of diabetes on either metformin or sulfonylurea monotherapy were assigned to combine the two (n = 2,227), or add ROSI (n = 2,220). The primary endpoint of the trial is hospitalization or death from any cause.

In this interim analysis, there was no statistically significant difference between the groups for CV mortality, MI, or all-cause mortality. The safety monitoring board of this trial, fully cognizant of the Nissen publication, did not feel that, based upon these prospective data, there is any safety concern sufficient to stop the trial. More conclusive information will be available at close of trial. ■

# Aldosteronism is a Frequent Cause of Resistant Hypertension in Diabetics

Umpierrez GE, et al. *Diabetes Care.* 2007;30(7):1699-1703.

Hypertension (HTN) is substantially more common in diabetics than in the general population. This is of particular concern since cardiovascular disease is also disproportionately the cause of death in persons with diabetes. Most diabetics have essential hypertension, but it is reasonable to suspect that resistant hypertension (defined as BP >140/90 despite at least 3 antihypertensive agents) in this population is sometimes caused by primary hyperaldosteronism (PHA). This report provides details about the prevalence of PHA in diabetics with resistant HTN.

The study population was comprised of diabetics with resistant HTN, who were allowed to continue their medications during the study. Persons already receiving aldosterone antagonists (ie, aldosterone, eplerenone) were excluded from the trial.

Screening lab data included a plasma aldosterone-to-renin ratio, which if abnormal, was followed by a salt loading test. PHA was considered confirmed if the 24-hr urine aldosterone on day 3 of salt loading was > 12 mcg, or if plasma aldosterone was > 5 ng/dL after a 4-hr IV saline load.

Ultimately, 14% of diabetics with resistant HTN were confirmed to have PHA. The authors suggest that screening for PHA is appropriate in the specific group of diabetics with resistant HTN. ■

# Hydroxychloroquine is Associated with Less Diabetes in RA

Wasko MCM, et al. *JAMA.* 2007;298(2):187-193.

Although rheumatoid arthritis (RA) immediately prompts consideration of joint disease and subsequent disabilities, lesser recognized is that persons with RA also suffer a disproportionate burden of cardiovascular disease. Of course, when a patient with RA develops diabetes, their CV risk is greatly magnified.

The antimalarials, of which hydroxychloroquine (HCQ) is an example, have been shown to improve insulin sensitivity and enhance insulin secretion. Indeed, hypoglycemia is a recognized adverse effect of antimalarials. Recently, a cluster of trials with medication, diet, and exercise have indicated that diabetes may be prevented by pharmacotherapies such as metformin, thiazolidinediones, and acarbose. The purpose of this publication by Wasko, et al was to compare the incidence of new onset diabetes in RA patients treated with HCQ (n = 1,808) vs. those on other regimens (n = 3,097) over an observation period of 21 years.

The incidence of new onset diabetes was 5.2/1000 patient-years in persons who received HCQ, compared to 8.9/1000 patient-years in the comparison group (p = <0.001). Longer HCQ use was associated with greater risk reductions. Although newer disease-modifying therapies for RA provide excellent therapeutic results, this advantage of hydroxychloroquine may prove to be very attractive for persons identified as high-risk for diabetes. ■

# The Safety and Efficacy of Our Newest Class of Pharmacotherapy for Diabetes: the Incretins

Amori RE, et all. *JAMA*. 2007;298(2):194-206.

Despite an increasing array of methods for control of diabetes, not even half of patients currently have attained and maintain an A1c less than 7%. Hence, new tools which may enhance achievement of goals are welcome, but only if the efficacy, safety, and tolerability is also acceptable. Because the incretins (ie, exenatide, sitagliptin) are typically weight-neutral, or even associated with weight loss, they are attractive to diabetic patients, many of whom struggle with weight management issues. This class of agents is complementary with many of the commonly used pharmacotherapies for diabetes. Currently, only one oral incretin (sitagliptin, trade name Januvia), and one parenteral incretin (exenatide, trade name Byetta) are available in the United States. Promising new delivery systems for exenatide, allowing once-weekly administration, and development of additional oral incretins (eg, vildagliptin) may provide even further diversity for this class of agents.

In this systematic review and meta-analysis, encompassing 29 clinical trials and over 20,000 study subjects, incretins were found to be comparably effective to other oral agents for lowering of glucose, with modest adverse effect profiles. Because there is a paucity of trials enduring past 30 weeks, true long-term safety remains to be determined. There are no large clinical trials of subjects treated with incretins to inform us of clinical endpoints such as diabetes-related death or cardiovascular disease. These data are reassuring that incretin therapy is safe and effective. ■

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# Optimum Duration of Treatment for Hepatitis C

Shifffman ML, et al. *N Engl J Med*. 2007;357:124-134.

Currently, we may be able to cure a substantial majority of persons with hepatitis C. Until very long-term data are available, the current gold standard for cure is sustained viral response (SVR), defined as an absence of detectible virus 6 months after cessation of treatment. The good news is that for persons with HCV genotype 2 or 3, a "traditional" regimen of 24 weeks treatment with peginterferon plus ribavirin produces a SVR in 80% of cases. Current treatment regimens are expensive and have adverse effects, so shortening the course, without compromising efficacy would be valuable.

Earlier data has shown that for HCV treatment subgroups that promptly clear HCV RNA (within 4 weeks), SVR is attained with as few as 12-16 weeks of treatment. To prospectively confirm that shorter treatment courses are as efficacious as longer, Shiffman, et al compared a 16-week course of therapy with a 24-week course in 1,469 study subjects.

The efficacy of the shorter course of therapy to achieve a SVR was significantly less than the longer course (62% vs 70%, $p < 0.001$). The "traditional" 24-week therapeutic course should remain standard for all but exceptional cases. ■

# Estrogen and Coronary Calcification

Manson JE, et al. *N Engl J Med*. 2007;356:2591-2602.

Analysis of data from the Women's Health Initiative (WHI) suggests that for younger women (age 50-59), the relationship between estrogen replacement and coronary health may not be the same as for the more mature women in this trial. Even though the overall "take-away" from the WHI is that women should not receive hormone replacement with hopes of reducing cardiovascular risk, reconsideration of subgroups suggests that older women (mean age of WHI participants = 63) respond differently than younger women.

The use of electron beam computed tomography (EBCT) to detect coronary calcium has been consistently supported as an accurate indicator of the presence of coronary calcification, and equally valid to exclude the same. Manson, et al performed an analysis of young women (age 50-59) from the WHI who underwent EBCT (or multidetector-row CT) at baseline and after 8.7 years. The treatment arm of the WHI actually lasted only 7.4 years, so the follow-up CT was obtained 1.3 years after the trial had concluded.

Coronary calcium scores were substantially lower among women who had received estrogen than placebo; for whom with the highest level of adherence to estrogen, the calcium scores were even lower. These data indicate that for younger women (age 50-59), estrogen replacement therapy is associated with lower frequency and level of coronary artery calcification, a respected surrogate for risk of myocardial infarction. ■