Drug Monitor

Losartan vs. Atenolol for Hypertension

According to a subgroup analysis of the multinational Losartan Intervention for Endpoint reduction in hypertension (LIFE) study, angiotensin II AT_1-receptor blockade with losartan is superior to beta-blockade with atenolol in preventing cardiovascular morbidity and mortality in patients with essential hypertension and left ventricular hypertrophy but no clinical evidence of vascular disease.

The analysis included 6,886 patients aged 55 to 80—nearly 75% of the total LIFE trial cohort. During a mean follow-up of 4.8 years, blood pressure dropped similarly and substantially in both the losartan and atenolol groups.

The primary composite endpoint of cardiovascular morbidity and mortality, however, was nearly 20% less common in patients given losartan than in those given atenolol. In addition, the relative risk of stroke (fatal or nonfatal) among patients taking losartan was 0.66. The differences between the groups with regard to cardiovascular death and myocardial infarction (MI) weren't significant. The incidence of new onset diabetes was 31% lower in the losartan group than in the atenolol group ($P < .001$).

In accordance with the findings of the entire LIFE sample, these results support the notion that interruption of the renin-angiotensin system provides clinical benefit beyond that attributable to blood pressure reduction. The significant reduction in stroke risk is particularly important, say the researchers, given that stroke was the most common component of the composite endpoint (occurring 44% more frequently than MI). The similar incidence of MI between the groups may indicate a balance between losartan's protection of coronary arteries from the direct toxic effects of angiotensin II and atenolol's greater reduction in myocardial oxygen demand.

Source: *Ann Intern Med.* 2003; 139:169–177.

Quinolones and Tendon Rupture

With a broad spectrum of activity, quinolones have become one of the most commonly prescribed antibacterial classes. But increasingly frequent reports of associated Achilles tendon ruptures and similar tendon problems raise questions about the level of risk to which patients taking these drugs are exposed. To learn more about this risk, a team of researchers from the Erasmus Medical Centre Rotterdam, the Utracht University, and the Hague, all in the Netherlands, and the Epidemiology and Pharmacology Information Core, London, England performed a population-based, case-control study using the General Practice Research Database in the United Kingdom between 1988 and 1998.

The researchers included only cases of first recorded Achilles tendon rupture for which at least 18 months of valid history prior to the event was available. Tendon ruptures due to major trauma were excluded. The control group consisted of a random sample of 50,000 patients from the database for whom at least 18 months of history prior to a randomly selected index date was available.

Overall, the adjusted odds ratio for Achilles tendon rupture was 4.3 among patients with current quinolone exposure, 2.4 among those with recent exposure, and 1.4 among those with past exposure. The risk was highest among the oldest current exposure patients, with an odds ratio of 20.4 in those aged 80 and older and 6.4 in those aged 60 to 79. The researchers say that approximately 2% to 6% of all Achilles tendon ruptures in people aged 60 and older can be attributed to quinolones.

They also found a strong dose-dependent relationship between quinolones and tendon rupture in this age group. At dosages above 1.25 times the defined daily dose (a standardized unit representing the average daily dose of each quinolone for an adult patient with the main indication), the odds ratio rose to 12.5 for patients aged 60 and older. Of the four quinolones studied, ofloxacin was associated with the highest risk of rupture, a finding consistent with those of earlier studies.

Concomitant use of corticosteroids increased the

odds of tendon rupture substantially. Adjusting for other independent risk factors (including osteoarthrosis, inflammatory joint diseases, gout, dialysis, and renal transplant), however, didn't change the risk estimates considerably.

The mechanism by which quinolones can affect tendon rupture risk isn't well understood, but it's known that quinolones have an affinity for connective tissues. While the researchers conclude that the absolute risk of Achilles tendon rupture is low, even among elders, they advise avoiding the combination of quinolones and oral corticosteroids or considering alternative antimicrobial agents.

Source: *Arch Intern Med.* 2003; 163:1801–1807.

NSAIDs and Parkinson's Disease

Could regular use of nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the risk of Parkinson's disease (PD)? Yes, by 45%, say researchers from the Harvard School of Public Health, Brigham and Women's Hospital and Harvard Medical School, and Massachusetts General Hospital in Boston, MA. Using data from the 142,902 participants of the prospective Health Professionals Follow-up Study and Nurses' Health Study, they examined the potential association between NSAID or aspirin use and PD risk.

The two studies, spanning 1980 through 2000, involved a series of mailed questionnaires asking participants about their health and medication usage. The responses showed that 415 participants developed PD—designated as the main outcome for this evaluation. The relative risk of PD was significantly lower with regular nonaspirin NSAID use than with nonregular use. And as duration of regular nonaspirin NSAID use increased, PD risk decreased. There was also a nonsignificant trend toward reduced PD risk with the use of two or more aspirin tablets per day.

Animal and postmortem studies have suggested that inflammation is involved in PD pathogenesis. The researchers also cite studies that have shown ongoing inflammatory reactions in the brain up to 16 years after patients develop parkinsonism. At lower dosages, aspirin has minimal anti-inflammatory effects, the researchers note, which might explain why low dose aspirin wasn't associated with reduced PD risk.

Source: *Arch Neurol*. 2003; 60:1059–1064.

Cautions About Clarithromycin for *H. Pylori*

Patients who have received macrolide antimicrobials and metronidazole may face a greater risk of infection with clarithromycin resistant *Helicobacter pylori*, say researchers from the CDC's Arctic Investigations Program in Anchorage, AK. Their study is, to their knowledge, the first to link previous antibiotic use to *H. pylori* resistance and subsequent treatment outcomes.

In their retrospective, cohort analysis of 125 Alaska Native adults with *H. pylori* infection, 83 (66%) had metronidazole resistant isolates and 37 (30%) had clarithromycin resistant isolates. Resistance to clarithromycin was associated with previous use of any macrolide antibiotic. Of the 37 patients with clarithromycin resistant *H. pylori*, 34 (92%) had been prescribed a macrolide in the previous 10 years, compared with 50 of the 88 patients (57%) with clarithromycin susceptible *H. pylori*. The percentage of infections with clarithromycin resistant strains increased with more frequent previous courses of macrolide treatment.

H. pylori resistance to metronidazole was associated with previous metronidazole use. More than half of patients with resistant isolates had been prescribed metronidazole, compared with only 10% of those with metronidazole susceptible isolates. The trend toward resistance held true even if metronidazole had been taken more than five years before the current infection.

Infection with clarithromycin resistant *H. pylori* was associated with a sixfold risk of treatment failure in patients given clarithromycin. Among the 53 patients given clarithromycin, treatment failed in 77% of those with clarithromycin resistant *H. pylori*, versus 13% of those with clarithromycin susceptible strains.

In a small, related study, researchers from University Hospital Uppsala, Sweden, and The Swedish Institute of Infectious Disease Control found that short-term treatment of *H. pylori* infection with a clarithromycin-based regimen can have long-term consequences on patients' indigenous microflora. All five consecutive patients who were treated with clarithromycin, metronidazole, and omeprazole for duodenal ulcers associated with *H. pylori* had evidence of high level clarithromycin resistance in their natural enterococci immediately after treatment, one year later, and even three years later. No such resistance was found in the five consecutive control patients who had dys-

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pepsia but no ulcer and weren't treated. Although antibiotic resistance among enterococci isn't tied to clinical problems, it potentially could result in interspecies transfer of resistance genes to invading organisms.

Sources: *Ann Intern Med.* 2003; 139:463–469.

Ann Intern Med. 2003;139: 483–487.

Antisuicide Advantage for Lithium?

Despite lithium's successful track record for long-term management of bipolar disorder, the number of prescriptions for this drug has declined over the past decade, while the use of anticonvulsants (such as divalproex) has increased steadily. Several studies have indicated lithium can reduce suicide risk in patients with bipolar disorders, but no large studies have examined divalproex's success in suicide prevention.

Prompted by this disparity, researchers from George Washington University Medical Center, Washington, DC; the Center for Health Outcome Research, Bethesda, MD; Kaiser Permanente Medical Care Program, Oakland, CA; and the Group Health Cooperative, Seattle, WA analyzed data on 20,638 patients enrolled in two West Coast managed care organizations who received either lithium, divalproex, or carbamazepine following a diagnosis of bipolar disorder. They found that the number of suicide attempts or deaths was one and a half to three times higher in patients taking divalproex than in those taking lithium.

After adjusting for age, sex, comorbid conditions, and use of other psychotropic drugs, the risk of suicide death was 2.7 times higher with divalproex than with lithium. The difference in risk between divalproex and lithium was consistent across all outcome measures: suicide death, attempt resulting in hospitalization, and attempt diagnosed in the emergency department.

The mechanism by which lithium might help prevent suicide attempts isn't clear, the researchers say, though the drug has been observed to reduce aggressive and impulsive behavior. They add that suicide is associated with reduced functional capacity of central serotonin systems, and that long-term lithium treatment enhances serotonin turnover.

Source: *JAMA.* 2003;290: 1467–1473.

Considerations in Simplifying HAART

Once your patient with HIV achieves sustained viral suppression, you may want to ease the burden of the highly active antiretroviral therapy (HAART) regimen by replacing the protease inhibitor (PI) with a drug (such as nevirapine, efavirenz, or abacavir) that has a simpler dosing schedule or fewer potential interactions. But before you do so, there are a number of factors to consider, say a team of Spanish researchers from the Nevirapine, Efavirenz, and Abacavir (NEFA) Study.

In this multicenter, open-label trial, the researchers enrolled 460 adults who were taking two nucleoside reverse-transcriptase inhibitors (NRTIs) and one PI, whose plasma HIV-1 RNA levels had stayed below 200 copies/mL for at least six months, and who wished to replace their PI for some reason. They randomly assigned the patients to switch their PI to either nevirapine (155 patients), efavirenz (156 patients), or abacavir (149 patients).

After 12 months, 117, 112, and 113 patients were still taking nevirapine, efavirenz, or abacavir, respectively. There was a trend toward more virologic failure in the abacavir group, compared to the nevirapine and efavirenz groups (16 patients versus eight and five, respectively). In addition, two abacavir patients had progressed to AIDS. On the other hand, the overall incidence of adverse events was significantly lower with abacavir (41%) than with the other two drugs (54% for nevirapine and 57% for efavirenz), and significantly fewer patients discontinued abacavir due to adverse events (9% compared to 26% for nevirapine and 27% for efavirenz). Regardless of drug group, a majority of the patients who experienced virologic failure with the study drug (79%) had received a suboptimal HIV regimen (consisting only of one or two NRTIs) in the past.

The researchers speculate that a factor in the abacavir group's higher rates of virologic failure could be cross-resistance between this drug and other NRTIs. They advise that simplifying HAART by replacing the PI is most likely to succeed in patients with no history of suboptimal therapy or virologic failure, particularly when the replacement drug is abacavir. ●

Source: *N Engl J Med*. 2003; 349:1036–1046.