

Barrett's Guidelines Lack Support in Practice

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SAN DIEGO — There is a lack of strong evidence to support the current screening and surveillance guidelines for Barrett's esophagus and associated neoplasia, Dr. Marcia Irene Canto said at a meeting jointly sponsored by the AGA Institute and the Japanese Society of Gastroenterology.

"Sedated esophagogastroduodenoscopy [EGD] screening may be more cost effective than surveillance only if Barrett's patients with dysplasia who are diagnosed by screening are followed," said Dr. Canto, director of clinical research in the division of gastroenterology and hepatology at Johns Hopkins University, Baltimore.

"The biopsy protocol detects cancer, but current guidelines regarding increased surveillance intervals in Barrett's patients without dysplasia would lead to missed high-grade dysplasia and cancer. We need better endoscopic techniques and better risk stratification," she said.

Current practices for screening and surveillance of Barrett's esophagus are not based on randomized, controlled trials (level I evidence) or even well-designed co-

hort or case-control trials (level II), she explained. They are based on decision analyses, case series, case reports, or flawed clinical trials (level III); opinions of expert authorities based on clinical evidence, descriptive studies, or reports of expert committees (level IV); and insufficient evidence to form an opinion (level V).

And it is probably cost effective to target patients with dysplastic Barrett's, she said. The evidence against surveillance is largely based on the fact that most Barrett's patients die from causes other than cancer. "When you look prospectively, the risk of cancer in Barrett's is low: about 0.5%-1.2% per year, so EGD, the standard way of doing surveillance, is very costly."

Moreover, "there is such inconsistency in techniques for surveillance. Many practicing gastroenterologists do not follow any par-

ticular biopsy or surveillance technique."

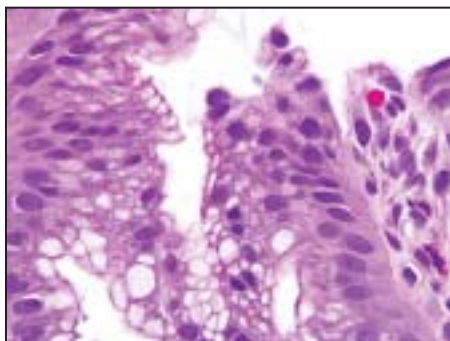
Since clinicians at Johns Hopkins began endoscopic surveillance in 1994, the prevalence of occult cancer in 39 Barrett's patients with high-grade dysplasia has decreased from 43% to 21%. None of the 15 patients who had some type of biopsy protocol or imaging technique implemented in their surveillance had occult cancer, whereas 8 of the 24 who did not follow a biopsy protocol had occult cancer. "This is even with modern endoscopy

techniques, so there is some benefit to trying to do that," Dr. Canto said.

For a Barrett's patient with no dysplasia, the American Gastroenterological Association (AGA) recommends a second EGD 1 year later, and then surveillance every 5 years (Gastroenterology 2005;128:1468-70).

The American College of Gastroenterology (ACG) guidelines are similar, but recommend surveillance every 3 years (Am. J. Gastroenterol. 2002;97:1888-95).

"Guidelines written by the GI societies



Patients with low-grade dysplasia, shown here, need an EGD every 6 months for a year.

COURTESY DR. MARCIA IRENE CANTO

"The rationale for screening and surveillance is to improve survival, but [increasingly], we are trying to prevent cancer in Barrett's patients. It's a different approach, by detecting high-grade dysplasia and intervening with ablation endoscopic mucosal resection or esophagectomy in this precancerous phase."

Data on 783 patients from five prospective studies and one patient registry suggest that the risk of cancer in Barrett's esophagus is related to the grade of dysplasia. The risk for patients with no dysplasia stands at 2%, and the risk for those with low-grade and high-grade dysplasia is 7% and 22%, respectively.

Dr. Canto noted that there are no randomized, controlled trials on the evidence for surveillance in Barrett's esophagus, only three retrospective case series and one ongoing prospective study. But data from those studies indicate that the 2-year survival rate seems better for patients who undergo surveillance, compared with those who do not (86% vs. 46%, respectively).

Newly published data vs rosuvastatin

As an adjunct to diet when diet alone is not

What mean LDL-C reduction did and rosuvastatin did not?

- ▶ VYTORIN 10/40 mg was superior to atorvastatin 40 mg at lowering LDL-C (57% vs 48%, $P<0.001$).¹
- ▶ VYTORIN 10/40 mg and 10/80 mg were both superior to atorvastatin 80 mg at lowering LDL-C (57% and 59% vs 53%, respectively, $P<0.001$).¹

*Mean percent change in LDL-C from untreated baseline in a multicenter, double-blind, randomized, active-controlled, 8-arm, parallel-group study (6 weeks of active treatment) (N=1,902). Patients with hypercholesterolemia who had not met their LDL-C goal as defined by NCEP ATP III were randomized to VYTORIN 10/10, 10/20, 10/40, or 10/80 mg or atorvastatin 10, 20, 40, or 80 mg. Mean pooled baseline LDL-C values for VYTORIN and atorvastatin were 178 mg/dL and 179 mg/dL, respectively. VYTORIN 10/10 mg reduced LDL-C by 47% from baseline vs 36% with atorvastatin 10 mg ($P<0.001$).¹

▶ The dosage should be individualized according to baseline LDL-C level, the recommended goal of therapy, and the patient's response.

VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated TOTAL-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia or mixed hyperlipidemia when diet alone is not enough.

Contraindications: hypersensitivity to any component of this medication; active liver disease; unexplained persistent elevations of serum transaminases; and women who are pregnant, nursing, or may become pregnant.

VYTORIN contains 2 active ingredients: ezetimibe and simvastatin.

No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

The clinical impact of comparative differences in lipid changes between products is not known.

SELECTED CAUTIONARY INFORMATION

Skeletal Muscle: Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy/rhabdomyolysis is dose related. Tell patients to promptly report muscle pain, tenderness, or weakness. Discontinue drug if myopathy is suspected or CPK levels rise markedly.

Myopathy Caused by Drug Interactions: Use of VYTORIN with itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided because of the increased risk of myopathy, particularly at higher doses.

VYTORIN vs atorvastatin¹
Significantly greater LDL-C reduction*

Treatment	Mean percent change in LDL-C from untreated baseline
VYTORIN 10/20 mg	51%
atorvastatin 10 mg	36%
atorvastatin 20 mg	44%

$P<0.001$



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are based on current data and decision analyses in terms of what the best surveillance interval is. There will never be the equivalent of the National Polyp Study for colon cancer surveillance," Dr. Canto said.

For a Barrett's patient with low-grade dysplasia, the AGA recommends an EGD every 6 months for 1 year, then increasing the surveillance interval to every 1-2 years. The ACG guidelines are similar, but recommend surveillance every year.

For a Barrett's patient with high-grade dysplasia, the American Society for Gastrointestinal Endoscopy recommends confirming the diagnosis with two experienced pathologists, then offering the

patient surgery or endoscopic therapy (Gastrointest. Endosc. 2006;63:570-80). The patient should undergo surveillance every 3 months for at least 2 years.

The ACG guidelines are similar but recommend endoscopic mucosal resection for more severe disease.

Preliminary results from a prospective multicenter study of 618 patients show that the prevalent cancer risk within 1 year of diagnosing the index lesion was 6.7% (Clin. Gastro. Hepatol. 2006;4:566-72). When the researchers followed the patients, the risk of cancer in patients with no dysplasia was 0.5% a year, and in those with low-grade dysplasia, it was similar, at 0.6% a year.

So far, regression of low-grade dysplasia has occurred in 66% of the patients. Dr. Canto pointed out that 53% of the incident high-grade dysplasias or cancers developed after two EGDs with no dysplasia.

"What if you have the patient back at year 5 according to the AGA guidelines, but the patient developed a Barrett's cancer or high-grade dysplasia in year 2? We don't have the evidence for increasing the surveillance intervals. In fact, preliminary evidence suggests Barrett's high-grade dysplasia or cancer might be missed if you followed the AGA guidelines."

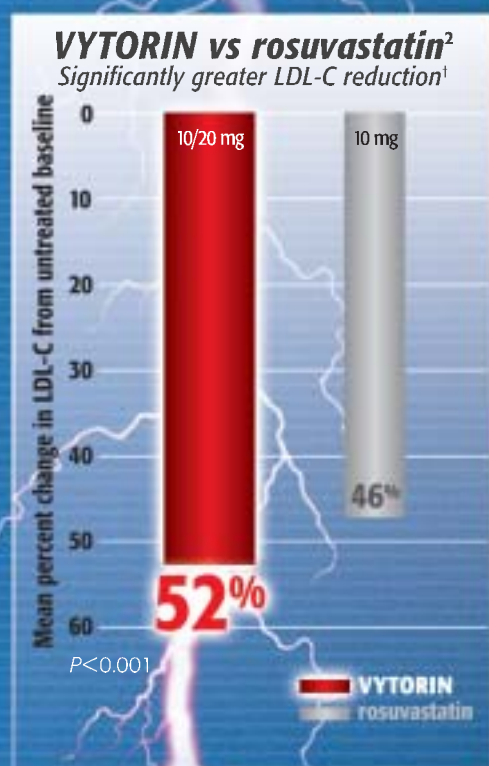
Screening for Barrett's esophagus and associated neoplasia presents another quag-

mire. ACG guidelines state that patients with chronic GERD symptoms are most likely to have Barrett's esophagus and should undergo upper endoscopy, but an AGA technical review concluded there is no direct evidence that has validated screening for esophageal cancer in the United States. This is in part because 40% of Barrett's patients with cancer have no GERD symptoms and fewer than 4% have Barrett's diagnosed before the cancer is diagnosed.

Endoscopic tools for screening include a standard videoendoscope (sedated or unsedated), an unsedated thin videoendoscope, an office-based thin battery-powered endoscope, and wireless capsule endoscopy. ■

enough, in 2 separate head-to-head studies

VYTORIN provide that atorvastatin
50% at a usual starting dose^{1,2,3}
 mean LDL-C reduction



➤ VYTORIN 10/40 mg lowered LDL-C more than rosuvastatin 20 mg (55% vs 52%, $P=0.001$).²

➤ VYTORIN 10/80 mg lowered LDL-C more than rosuvastatin 40 mg (61% vs 57%, $P<0.001$).²

[†] Data from a multicenter, randomized, double-blind, active-controlled, 6-arm, parallel-group study designed to evaluate the efficacy and safety of VYTORIN vs rosuvastatin over a 6-week period. Patients with hypercholesterolemia (N=2,959) were randomized to 1 of 6 treatment groups: VYTORIN 10/20, 10/40, or 10/80 mg or rosuvastatin 10, 20, or 40 mg. Mean baseline LDL-C level for both VYTORIN 10/20 mg and rosuvastatin 10 mg was 172 mg/dL.²

SELECTED CAUTIONARY INFORMATION (cont)

The concomitant use of VYTORIN and fibrates (especially gemfibrozil) should be avoided. Although not recommended, the dose of VYTORIN should not exceed 10/10 mg if used with gemfibrozil. The benefit of further alterations in lipid levels by the combined use of VYTORIN with niacin should be carefully weighed against the potential risks of myopathy. The dose of VYTORIN should not exceed 10/10 mg daily in patients receiving cyclosporine or danazol, and 10/20 mg daily in patients receiving amiodarone or verapamil.

Liver: It is recommended that liver function tests be performed before the initiation of treatment and thereafter when clinically indicated. Additional tests are recommended prior to and 3 months after titration to the 10/80-mg dose, and semiannually for the first year thereafter.

VYTORIN is not recommended in patients with moderate or severe hepatic insufficiency.

In clinical trials, the most commonly reported side effects, regardless of cause, included headache (6.8%), upper respiratory tract infection (3.9%), myalgia (3.5%), influenza (2.6%), and extremity pain (2.3%).

Please read the brief summary of Prescribing Information on the adjacent page.

References: 1. Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VIVA) Study. *Am Heart J*. 2005;149:464-473. 2. Catapano AL, Davidson MH, Ballantyne CM, et al. Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients. *Curr Med Res Opin*. 2006;22:2041-2053. 3. IMS HEALTH, NPA PlusSM, NRx, July 2006.

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VYTORIN
 (ezetimibe/simvastatin)
 tablets