Guidelines Focus: Cardiovascular Prevention and Cholesterol Guidelines

Following a National Heart, Lung, and Blood Institute (NHBLI) announcement earlier this year that it would no longer issue guidelines but instead, provide support for guidelines produced by other organizations, the American Heart Association (AHA) and the American College of Cardiology (ACC) took over publication of the guidelines and recently released four new clinical practice guidelines for: assessment of cardiovascular risk, management of blood cholesterol, management of overweight and obesity in adults, and lifestyle modifications to reduce cardiovascular risk. Prescribers are advised to use a new online risk calculator that predicts risk for myocardial infarctions and strokes. This replaces the prior Framingham risk assessment tool that focused on coronary heart disease. Controversy surrounds the new risk calculator, as it appears to overestimate risk. The guideline specifically recommends against the routine use of carotid intima-medial thickness (CIMT). It is a useful research tool but broader use is not warranted because of the large amount of inter- and intra-operator variability. The cholesterol guidelines replace the older Adult Treatment Panel (ATP-3) cholesterol guidelines. The new guidelines emphasize an assessment of risk, and that statin and lifestyle treatment should be aimed to reduce risk, not just an isolated LDL cholesterol number. LDL cholesterol remains important but the guidelines state that statins do not simply treat cholesterol; rather they are risk-reducing agents. Based on a systematic evidence review, the expert panel found no evidence supporting the use of fixed LDL cholesterol or non-HDL cholesterol goals to guide therapy. The lipid guideline identifies four groups for whom statin therapy is recommended:

- Patients with atherosclerotic cardiovascular disease
- Patients with extremely high cholesterol levels (LDL cholesterol >190 mg/dL or familial hypercholesterolemia)
- Patients who are between 40 and 75 years of age and are diabetic
- Patients with an estimated 10-year cardiovascular disease risk of ≥7.5% and who are between 40 and 75 years of age

The guideline recommends high-intensity statin therapy for the first two groups. The last two groups are suitable for moderate-intensity therapy, though some patients with type 2 diabetes may benefit from high-intensity therapy. High-intensity statin therapy lowers LDL cholesterol by approximately ≥50%. Moderate-intensity statin therapy lowers LDL cholesterol by approximately 30% to less than 50%. The new guidelines do not endorse the routine use of non-statin therapies due to the lack of effectiveness for prevention of heart attacks and strokes. The guidelines recommend screening for new onset diabetes in patients receiving statins. No recommendations were made regarding initiation or continuation of statin therapy for patients with heart failure or on hemodialysis. The new obesity guidelines do not include pharmacotherapy, so the two new obesity drugs, phentermine/topiramate extended-release (Qsymia™) and lorcaserin (Belviq®), are not addressed.

Guidelines Focus: Hypertension Algorithm

Hypertension guidelines, to succeed the JNC-7 guideline, are not expected to be published by the AHA/ACC until 2014. In the meantime, the AHA/ACC, in conjunction with the Centers for Disease Control and Prevention (CDC), have introduced a hypertension science advisory, developed primarily to be part of an overall systems approach for primary care clinicians, to enhance the detection and control of hypertension. Hypertension currently affects nearly 78 million adults in the U.S. and is also a major modifiable risk factor for other cardiovascular diseases and stroke. The AHA has made hypertension a primary focus area of its 2014–2017 strategic plan, as it seeks to improve the cardiovascular health of all Americans by 20% and reduce the death rate from cardiovascular disease and stroke by 20% by 2020. Similarly, Million Hearts, a U.S. Department of Health and Human Services initiative spearheaded by the CDC and the Centers for Medicare and Medicaid Services (CMS) to prevent a million heart attacks and strokes by 2017, has focused its first 2 years on actions to improve and achieve control of hypertension. The AHA/ACC/CDC treatment algorithm eliminates the prehypertension category. Stage 1 hypertension is defined as systolic blood pressure of 140–159 or diastolic blood pressure of 90–99 mmHg. Lifestyle modifications are first-line therapy for any stage of hypertension. A thiazide diuretic may be considered for initial pharmacotherapy for stage 1 hypertension. Stage 2 hypertension is classified as systolic blood pressure over 160 mmHg or diastolic blood pressure over 100 mmHg. For stage 2 hypertension, in addition to lifestyle modifications, a thiazide diuretic and another agent (two-drug regimen is preferred), either an ACE inhibitor (ACEI), an angiotensin-receptor blocker (ARB), or a calcium-channel blocker (CCB) should be prescribed. An ACEI/CCB combination may also be considered. The science advisory also offers suggestions for choosing drugs in the presence of certain medical conditions and provides a brief summary of the benefits of lifestyle modifications.

Complete Phase-Out of Chlorofluorocarbon (CFC) Inhalers

The FDA will complete its phase-out of all inhaler medical products containing CFCs by December 31, 2013. This effort is to comply with an international treaty to protect the ozone layer by phasing out the global production of numerous substances, including CFCs, which contribute to ozone depletion. Most inhalers containing CFCs have already been phased out by the FDA, but Combivent® Inhalation Aerosol, ipratropium and albuterol, and Maxair® Autohaler, pirbuterol, remain, but will no longer be available after the end of this year. Boehringer Ingelheim announced that Combivent Inhalation Aerosol was discontinued in July 2013; Combivent® Respinimat® is available as a replacement for Combivent.

Sources:
www.ashp.org
www.cdc.gov
www.fda.gov
www.medscape.com
www.PTCommunity.com
www.pubmed.gov

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Drug Information Highlights

- In August 2012, Teva received approval for a short-acting granulocyte colony stimulating factor (G-CSF) tbo-filgrastim, Granix™. On November 10, 2013, Teva launched this branded biologic copy to Amgen’s brand filgrastim, Neupogen®. This is the first new G-CSF to the U.S. market in more than ten years. Granix, formerly known as Neutroval, is not considered a biosimilar as it did not receive approval via the biosimilar pathway. Teva pursued approval through submitting a Biologics License Application (BLA). Granix is also not considered interchangeable with Neupogen. Under a settlement reached between Teva and Amgen, Teva was permitted to market Granix as well as filgrastim (Neugranin), a longer lasting fusion of G-CSF and human serum albumin. However, Teva withdrew the BLA for filgrastim, its version of pegfilgrastim (Neulasta®), from the Food and Drug Administration (FDA) review process due to the need for more confirmatory data. Granix is approved for chemotherapy-induced neutropenia prophylaxis to reduce the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia. It is available as 300 mcg/0.5 mL and 480 mcg/0.8 mL single-use prefilled syringes for subcutaneous injection by a health care professional.

- Health care professionals are being advised to carefully consider the timing of spinal catheter placement and removal in patients taking anticoagulants, such as enoxaparin (Lovenox®), to decrease the risk of spinal column bleeding and subsequent paralysis after spinal injections, including epidural procedures and lumbar punctures. The FDA is continuing to evaluate the safety of other anticoagulants.

- Abbott Diabetes Care has issued a voluntary recall on 20 lots of FreeStyle® and FreeStyle Lite® blood glucose test strips. They produce erroneously low blood glucose results when used with FreeStyle® blood glucose meters, FreeStyle Flash® blood glucose meters, and the FreeStyle® blood glucose meter built into the OmniPod® system. Abbott Diabetes Care will replace the affected test strips for patients who have been impacted.
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Description</th>
<th>Applicant</th>
<th>FDA Status</th>
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<tbody>
<tr>
<td>lipid injectable emulsion</td>
<td>Clinolipid</td>
<td>Baxter’s 20% lipid injectable emulsion (Clinolipid) has received approval for intravenous (IV) parenteral nutrition in adults. Clinolipid, which is a mixture of refined olive and refined soybean oils, was approved under a priority review to help alleviate a short supply of injectable lipid emulsions. The recommended dose depends on energy expenditure, clinical status, body weight, tolerance, ability to metabolize and consideration of additional energy given to the patient. Clinolipid should be used with caution in patients with pre-existing liver disease or liver insufficiency. Clinolipid is not indicated for use in preterm infants or other pediatric patients and carries a warning about the risk of death in preterm infants. According to the American Society for Parenteral and Enteral Nutrition (ASPEN), there has been an ongoing shortage of many components of IV parenteral nutrition, including a shortage of IV fat emulsions (IV lipids). The FDA approved Clinolipid to alleviate shortages of injectable lipid emulsions.</td>
<td>Baxter Healthcare</td>
<td>NDA Approval 10/03/2013</td>
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<td>obinutuzumab</td>
<td>Gazyva™</td>
<td>Obinutuzumab (Gazyva) is the first drug with “breakthrough” therapy designation to receive FDA approval. It has been approved for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). In the pivotal study that led to its approval, the median progression free survival (PFS) in the obinutuzumab in combination with the chlorambucil arm was 23 months and 11.1 months in the chlorambucil alone arm. Obinutuzumab is an anti-CD20 monoclonal antibody and carries a boxed warning regarding possible hepatitis B virus reactivation and progressive multifocal leukoencephalopathy. Patients are premedicated with glucocorticoid, acetaminophen, and antihistamine. Administer obinutuzumab by intravenous infusion only. Administration via IV push or IV bolus is not recommended. Obinutuzumab is to be given for six cycles (28-day cycles) in doses of 100 mg on day 1 of cycle 1, 900 mg on day 2 of cycle 1, 1,000 mg on days 8 and 15 of cycle 1, and 1,000 mg on day 1 of cycles 2–6. It is available as 1,000 mg/40 mL (25 mg/mL) in a single use vial. The solution for infusion should be prepared using aseptic technique and diluted in 0.9% sodium chloride in a volume as determined by the dose being administered. Obinutuzumab should only be administered by a health care professional.</td>
<td>Genentech</td>
<td>BLA Approval 11/01/2013</td>
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<tr>
<td>eslicarbazepine acetate</td>
<td>Aptiom®</td>
<td>Eslicarbazepine acetate (Aptiom), a voltage gated sodium channel blocker, is indicated for the treatment of partial onset seizures in adults with epilepsy. Patients should be monitored for increased depression and suicidal ideation or other changes in mood. The initial dose is 400 mg once daily for one week, increased to a maintenance dose of 800 mg once daily. The maximum recommended dose is 1,200 mg daily, which can be started after one week of a maintenance dose of 800 mg. Patients with moderate to severe renal impairment, should be initiated at 200 mg once daily for two weeks. The dosage can then be increased to maintenance dose of 400 mg once daily for a maximum recommended dose of 600 mg daily. Aptiom will be available in 200 mg, 400 mg, 600 mg, and 800 mg tablets in second quarter of 2014.</td>
<td>Sunovion</td>
<td>NDA Approval 11/08/2013</td>
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<tr>
<td>ibrutinib</td>
<td>Imbruvica™</td>
<td>Ibrutinib (Imbruvica) was approved for the treatment of mantle cell lymphoma, a rare and aggressive form of non-Hodgkin lymphoma, in patients who have received at least one prior therapy. Patients should be monitored for bleeding, fever, and infections. Complete blood counts should be checked monthly. Common adverse reactions include thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, and nausea. This kinase inhibitor is dosed 560 mg (four 140 mg capsules) once daily with a glass of water, preferably around the same time every day. The 140 mg capsules should not be opened, broken, or chewed.</td>
<td>Pharmacyclics/ Janssen</td>
<td>NDA Approval 11/13/2013</td>
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<td>luliconazole</td>
<td>Luzu™</td>
<td>Luliconazole (Luzu) cream, an azole antifungal, is FDA approved for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by Trichophyton rubrum and Epidermophyton floccosum in patients 18 years of age and older. For the treatment of interdigital tinea pedis, luliconazole is applied to the affected area and one inch surrounding the area once daily for two weeks. When treating tinea cruris or tinea corporis, it is applied to the affected area and one inch surrounding the area once daily for one week. It is available as a 1% topical cream containing 10 mg of luliconazole.</td>
<td>Valeant</td>
<td>NDA Approval 11/14/2013</td>
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<tr>
<td>sorafenib</td>
<td>Nexavar®</td>
<td>The FDA approved the use of sorafenib (Nexavar) for an expanded indication to treat a locally recurrent or metastatic, progressive, differentiated thyroid cancer that can no longer be treated with radioactive iodine. The oral kinase inhibitor is already approved for the treatment of unresectable hepatocellular carcinoma and advanced renal cell carcinoma (RCC). The recommended dose for all indications is 400 mg (two 200 mg tablets) twice daily orally without food, at least one hour before or two hours after a meal.</td>
<td>Bayer</td>
<td>NDA Approval 11/22/2013</td>
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