National Lipid Association: New Guidance on Dyslipidemia

Several organizations have issued guidelines for the management of dyslipidemia and, although there are many commonalities, there are some differences. The National Lipid Association (NLA) has published Part 1 of their new guidelines for the management of dyslipidemia. Part 2 is currently under development and will include areas such as lifestyle therapies, special populations, patient adherence, and team-based collaborative care. In Part 1, the NLA outlines a patient-centered approach based on atherosclerotic cardiovascular disease (ASCVD) risk assessment. As other organizations, the NLA emphasizes lifestyle therapies as an important aspect of ASCVD risk-reduction.

The NLA recommends lipid levels be used in conjunction with other ASCVD risk factors to assess overall risk. They also consider the use of risk calculators, such as the National Heart, Lung, Blood Institute’s (NHLBI) Adult Treatment Panel III (ATP III) Framingham Risk Score and the American College of Cardiologist (ACC)/American Heart Association’s (AHA) 2013 Pooled Cohort Equations.

While most organization use low density lipoprotein cholesterol (LDL-C) level as the primary target of lipid lowering therapy, the NLA considers non-high density lipoprotein cholesterol (non-HDL-C) to be superior to LDL-C for predicting ASCVD event risk because non-HDL-C is more correlated with apolipoprotein B (Apo B), and is more closely associated with the total burden of atherogenic particles. The NLA now uses non-HDL-C measurements along with LDL-C as primary targets of therapy. Triglyceride level is associated with the very low density lipoprotein cholesterol (VLDL-C) level; therefore, using non-HDL-C as a target also simplifies the management of patients with high triglycerides. Desirable targets in patients with low, moderate, and high risk of ASCVD event are non-HDL-C < 130 mg/dL and LDL-C < 100 mg/dL; in patients considered to be at very high risk, target measures are less than 100 mg/dL and 70 mg/dL, respectively.

The NLA advises that intensity of risk-reduction therapy should be based on the patient’s absolute risk for an ASCVD event. The NHL recommends for patients at low and moderate ASCVD event risk, lifestyle therapies, such as diet modification and moderate physical activity before initiating drug therapy. For patients at high or very high risk, drug therapy may be prescribed from the start. For patients in whom drug therapy is indicated, moderate to high intensity statin therapy is considered first-line. Non-statin agents, such as cholesterol absorption inhibitors, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid can be considered in patients with contraindications or intolerance to statin therapy, or as add-on if atherogenic cholesterol levels remain elevated with maximally tolerated statin doses. If very high triglycerides (≥ 500 mg/dL) exist, a triglyceride-lowering drug may be considered for first-line use to prevent pancreatitis. Response and adherence to therapy should be monitored every four to twelve months.

In comparison, the ATP III 2004 guidelines recommend LDL-C as primary target of therapy assessment. In high-risk patients, the recommended goal is LDL-C < 100 mg/dL, but, if risk is very high, an LDL-C < 70 mg/dL is an option. In high- and moderately high-risk patients, the intensity of therapy should be sufficient to achieve at least a 30 to 40 percent LDL-C reduction. The ACC/AHA 2013 guidelines...
advise prescribers to use the Pooled Cohort Equations to evaluate sex- and race-specific estimates of 10-year risk of ASCVD. However, controversy surrounds this new risk calculator, as it appears it may overestimate risk. ACC/AHA supports the use of a percent reduction in LDL-C, rather than a specific LDL-C level to assess therapeutic response to statin therapy. In addition, ACC/AHA states that, in general, non-statin agents do not provide acceptable ASCVD risk-reduction benefits as compared to statins; however, these agents may be added if maximum intensity statin therapy has not achieved desired response.

**ACC/AHA and Non-ST-Elevation Acute Coronary Syndromes**

The American College of Cardiology (ACC) and the American Heart Association (AHA) released new practice guidelines for the management of patients with non-ST-elevation acute coronary syndromes (NSTE-ACS). The majority of patients who present with acute coronary syndrome (ACS) have unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI). Since the presentation of these conditions is similar, the ACC/AHA now refers to both as NSTE-ACS. The document replaces their 2007 guideline and the 2012 focused update.

In the 2014 guidance, the general management approach remains the same including risk stratification, use of medical therapy and revascularization, and the need for secondary preventive therapies. Although NSTE-ACS patients with significant coronary disease are generally eligible for an early invasive strategy, some low-risk patients may be eligible for medical therapy. ACC/AHA now includes an “ischemia-guided” strategy which seeks to avoid the routine early use of invasive procedures unless patients experience refractory or recurrent ischemic symptoms or develop hemodynamic instability. An ischemia-guided approach is recommended for patients with low-risk scores (TIMI 0 or 1, GRACE < 109).

Invasive strategies, diagnostic angiography with intent to perform revascularization, if needed, are categorized based on timing: immediate (within two hours), early (within 24 hours), and delayed (25 to 72 hours). Patients in need for immediate invasive strategy have refractory or recurrent angina, symptoms of heart failure, mitral regurgitation, hemodynamic instability, and sustained ventricular tachycardia or fibrillation. Those in need of early intervention have a GRACE risk score > 140 or temporal change in tropin or new ST depression. Delayed intervention is appropriate in patients with renal insufficiency, left ventricular ejection fraction (LVEF) < 40%, early post-infarct angina, history of percutaneous coronary intervention (PCI) within the past six months, prior coronary artery bypass surgery (CABG), GRACE risk score of 109-140, or TIMI score of ≥ 2.

Relevant changes regarding medical therapy include a class IIa recommendation for the use of ticagrelor (Brilinta®) over clopidogrel; previously, both agents were given a class I recommendation, with a higher level of evidence rating given to clopidogrel. Ticagrelor and prasugrel (Effient®) are preferred over clopidogrel, prior to PCI (Class IIa); however, prasugrel should not be used in patients who are at high risk for bleeding, such as age ≥ 75 years, body weight < 60 kg, or a history of stroke or transient ischemic attack. For patients undergoing PCI who have received a loading dose of clopidogrel 300 mg, a second dose should be administered prior to the procedure. Prior to CABG, aspirin should be continued or administered; clopidogrel or ticagrelor should be discontinued. Therapy with a proton pump inhibitor (PPI), except esomeprazole and omeprazole, is recommended in patients receiving triple oral antithrombotic therapy. The ACC/AHA also addresses pain management in the post-MI patient. If chronic pain management is necessary, acetaminophen and nonacetylated salicylates (choline magnesium trisalicylate, salsalate) or tramadol should be tried before a low dose narcotic. If a low dose narcotic is not effective, then a non-selective nonsteroidal anti-inflammatory drug (NSAID), such as naproxen, can be used. A selective COX-2 inhibitor is only recommended as a last option. Finally, ACC/AHA includes a new class I recommendation pertaining to patient hospital discharge and the importance of a smooth transition of care to home.

**ASCO New Guidelines for the Treatment of Prostate Cancer**

The American Society of Clinical Oncology (ASCO) published joint practice guidelines with Cancer Care Ontario (CCO) on the treatment of men with metastatic castration-resistant prostate cancer (CRPC). Recommendations were based on improved survival and/or quality of life (QoL) and include six new treatments that have been FDA approved in recent years. Recommended therapies which demonstrated improved survival and QoL include oral abiraterone (Zytiga®)/prednisone or enzalutamide (Xtandi®); intravenous radium-223 in men with bone metastases; and intravenous docetaxel plus prednisone. Therapies that have demonstrated improved survival, but not improved QoL, are sipuleucel-T (Provenge®) intravenous infusion in men with minimal or no symptoms and cabazitaxel (Javtau®) intravenous infusion plus prednisone if disease progresses despite docetaxel therapy. Therapy with mitoxantrone plus prednisone has demonstrated QoL benefit but not improved survival. Other key recommendations include: continuation of androgen deprivation therapy via pharmaceutical or surgical modalities, indefinitely regardless of additional therapies, and palliative care should be offered to all patients.
Long-Term Weight Gain Following Antidepressant Use

Studies suggest that antidepressants are associated with modest weight gain with short-term use, but little is known about longer-term effects and differences between individual medications in general clinical populations. Because more than ten percent of Americans are prescribed antidepressants at any given time, the potential health consequences could be substantial. Obesity has been associated with higher incidence of cardiovascular disease, type 2 diabetes mellitus, hypertension, stroke, dyslipidemia, osteoarthritis, and some cancers, as well as significantly reduced life expectancy and increased all-cause mortality. Differences between medication classes in their propensity to cause weight gain have been reported. Early studies suggested older antidepressants, including the tricyclic antidepressants, monoamine oxidase inhibitors [MAOls], and the atypical antidepressant mirtazapine, were more likely to cause weight gain than selective serotonin reuptake inhibitors (SSRIs) or other new antidepressants.

In a recent analysis published in the Journal of the American Medical Association, electronic health records of 22,610 patients taking various antidepressants were used to evaluate for weight gain over a 12 month period. The antidepressants in this review included amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, mirtazapine, nortriptyline, paroxetine, venlafaxine, and sertraline. The greatest increase in weight was identified with mirtazapine (0.5-0.75 percent), paroxetine (0.25-0.5 percent), and citalopram (0.25-0.5 percent). Alternatively, results showed the least weight gain with patients taking bupropion (< 0.25 percent) and fluoxetine (0.25 percent). With the increased utilization of antipsychotics and their tendency to have significant increases on weight gain, an additional analysis was conducted. When those individuals taking concomitant antipsychotic therapy were excluded from the analysis, the results did not change significantly. Overall, the differences between antidepressants to cause weight gain are relatively modest, but this analysis does show that some SSRIs may result in weight gain similar to older antidepressants. If weight gain is of particular concern, this data can guide clinicians when making individualized treatment choices for their patients.

Paliperidone Palmitate (Invega®, Sustenna®) and Haloperidol Decanoate for Maintenance Treatment of Schizophrenia

Long-acting injectable antipsychotic agents are prescribed to reduce nonadherence and relapse in individuals diagnosed with schizophrenia-spectrum disorders. Long-acting injectable versions of older antipsychotic medications have been available for decades, but their use has been limited, in part due to their propensity to cause extrapyramidal symptoms, including tardive dyskinesia. The relative effectiveness of long-acting injectable versions of second-generation and older antipsychotic agents has not been evaluated. In recent years, head-to-head trials and meta-analyses have called into question the advantages of using second generation antipsychotic medications over older injectable antipsychotics.

The goal of this randomized, double-blind, study was to compare the effectiveness of the second-generation long-acting injectable antipsychotic paliperidone palmitate with the older long-acting injectable antipsychotic haloperidol decanoate. Study participants included 311 adults diagnosed with schizophrenia or schizoaffective disorder who were clinically assessed to be at risk of relapse and likely to benefit from a long-acting injectable antipsychotic. This study used intramuscular injections of haloperidol decanoate 25 mg to 200 mg or paliperidone palmitate 39 mg to 234 mg every month for up to 24 months. Efficacy failure was defined as a psychiatric hospitalization, a need for crisis stabilization, a substantial increase in frequency of outpatient visits, or a clinician’s decision that an oral antipsychotic could not be discontinued within eight weeks after starting the long-acting injectable antipsychotic.

Statistically significant differences in the rate of efficacy failure for paliperidone palmitate compared with haloperidol decanoate were not found. On average, paliperidone was associated with weight gain, while haloperidol was associated with weight loss. Greater increases in serum prolactin were reported with paliperidone and haloperidol decanoate was associated with more akathisia. The results of this study are similar to previous studies which did not find large differences in effectiveness between typical and atypical antipsychotics.
## Recent FDA Approvals

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Description</th>
<th>Applicant</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ferric citrate</td>
<td>no trade name</td>
<td>Ferric citrate, a phosphate binder formerly known as Zerenex™, received FDA approval for the control of serum phosphorus levels in patients with chronic kidney disease who are on dialysis. Recommended initial dose is two tablets three times daily with meals. Dose can be adjusted to achieve desired phosphorus level, up to 12 tablets per day. Tablets contain 1 g ferric citrate, equivalent to 210 mg ferric iron. To avoid iron overload patient should be monitored for ferritin and transferrin saturation (TSAT).</td>
<td>Keryx</td>
<td>FDA NDA approval 09/05/2014</td>
</tr>
<tr>
<td>naltrexone/ bupropion</td>
<td>Contrave®</td>
<td>A combination of naltrexone, an opioid antagonist, and bupropion, an antidepressant, Contrave, was FDA approved as an adjunct to diet and exercise for chronic weight management in obese (Body Mass Index [BMI] ≥ 30 kg/m²) or overweight (BMI ≥ 27 kg/m²) adults who have at least one weight-related comorbidity such as hypertension, type 2 diabetes, or high cholesterol. Contrave carries a boxed warning for increased risk of suicidal thoughts and serious neuropsychiatric reactions. Contraindications for use include uncontrolled hypertension, seizure disorder, and chronic opioid use. Contrave dose is escalated to reach two tablets each twice daily by week four. It is available as an extended-release tablet containing 8 mg naltrexone and 90 mg bupropion.</td>
<td>Orexigen</td>
<td>FDA NDA approval 09/10/2014</td>
</tr>
<tr>
<td>immune globulin infusion 10% (human) with recombinant human hyaluronidase</td>
<td>Hyqvia™</td>
<td>Immune globulin 10%/recombinant human hyaluronidase (Hyqvia) is indicated for the treatment of primary immunodeficiency (PI) in adults. Hyqvia can be given by a healthcare professional or by self-administration after adequate training. After initial titration as outlined in the package insert, the recommended target dosage is 300 - 600 mg/kg by subcutaneous infusion every three to four weeks. The components of Hyqvia are administered sequentially, beginning with recombinant human hyaluronidase. Hyqvia carries an immune globulin class black box warning of thrombosis.</td>
<td>Baxter</td>
<td>FDA BLA approval 09/12/2014</td>
</tr>
<tr>
<td>naloxegol</td>
<td>Movantik™</td>
<td>The FDA approved naloxegol (Movantik), a peripherally-acting opioid receptor antagonist, for the treatment of opioid-induced constipation in adults with chronic non-cancer pain. It is a controlled substance schedule II; although has no risk of abuse of dependency. The recommended dose is 25 mg daily in the morning on an empty stomach. If 25 mg dose is not tolerated, it can be decreased to 12.5 mg. Available doses include 12.5 mg and 25 mg tablet. Adverse events include abdominal pain, diarrhea, and nauscea.</td>
<td>AstraZeneca</td>
<td>FDA NDA approval 09/16/2014</td>
</tr>
<tr>
<td>dulaglutide</td>
<td>Trulicity™</td>
<td>Dulaglutide (Trulicity), a SC glucagon-like peptide-1 (GLP-1) receptor agonist, was approved as an adjunct to diet and exercise for the management of type 2 diabetes. Dulaglutide carries a boxed warning for the risk of thyroid C-cell tumors. Pancreatitis has also been reported with its use. The initial dosage is 0.75 mg SC in the abdomen, thigh, or upper arm once weekly. The maximum recommended dose is 1.5 mg weekly. Dulaglutide will be available as 0.75 mg/0.5 mL and 1.5 mg/0.5 mL single-dose pens and prefilled syringes.</td>
<td>Eli Lilly</td>
<td>FDA BLA approval 09/18/2014</td>
</tr>
<tr>
<td>cobicistat</td>
<td>Tybost™</td>
<td>The FDA has approved cobicistat (Tybost), a P450 CYP3A enzyme inhibitor, as a boosting agent to increase systemic exposure of atazanir (Reyataz®) or darunavir (Prezista®) used in combination with other retrovirals to treat HIV. It is given as 150 mg once daily with atazanavir or darunavir and with food. Cobicistat will be available as a 150 mg tablet. Previously, cobicistat was available only as a component of Striibild®, a four-drug combination of cobicistat, elvitegravir, emtricitabine, and tenofovir.</td>
<td>Gilead</td>
<td>FDA NDA approval 09/24/2014</td>
</tr>
<tr>
<td>elvitegravir</td>
<td>Vitekta™</td>
<td>Elvitegravir (Vitekta) is an integrase strand transfer inhibitor indicated for treatment-experienced HIV-positive patients, to be used in combination with a protease inhibitor coadministered with ritonavir plus one or more HIV antiretroviral agents. It is administered once daily with food. Available in 85 mg or 150 mg tablets, previously elvitegravir was only a component of Striibild®.</td>
<td>Gilead</td>
<td>FDA NDA approval 09/24/2014</td>
</tr>
<tr>
<td>tiotropium</td>
<td>Spiriva® Respimat®</td>
<td>The FDA has approved the anticholinergic agent, tiotropium, as a metered spray inhaler (Spiriva Respimat) for the maintenance treatment of COPD. The recommended dosage is two puffs once daily. Spiriva Respimat is expected to be available in January 2015 as a carton containing one cartridge and one Respimat inhaler (60 metered actuations). Each actuation delivers 2.5 mcg tiotropium (equivalent to 3.124 mcg tiotropium bromide monohydrate).</td>
<td>Boehringer Ingelheim</td>
<td>FDA NDA approval 09/24/2014</td>
</tr>
</tbody>
</table>

### References
- [www.cdc.gov](http://www.cdc.gov)
- [www.drgov](http://www.drgov)
- [www.fda.gov](http://www.fda.gov)
- [www.heart.org](http://www.heart.org)
- [www.jama.com](http://www.jama.com)
- [www.medscape.com](http://www.medscape.com)
- [http://jama.jamanetwork.com/journal.aspx](http://jama.jamanetwork.com/journal.aspx)
- [http://www.cdc.gov](http://www.cdc.gov)
- [http://www.heart.org](http://www.heart.org)