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Topics Covered in This Issue

Updated AACE/ACE Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease

Introduction

- In 2017, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) release guidelines for management of dyslipidemia and prevention of atherosclerotic cardiovascular disease (ASCVD). The update incudes 87 recommendations for dyslipidemia and ASCVD management, including a new cardiovascular risk category. This newsletter will highlight their risk assessment methods and lipid-lowering therapy recommendations.

Risk Assessment

- The guidelines outline numerous additional and non-traditional risk factors for ASCVD, but the major independent risk factors they use to determine a patient's ASCVD risk category are as follows:

Major Risk Factors

- Age (men ≥45; women ≥55 years)
- High serum low-density lipoprotein (LDL)
- Low serum high-density lipoprotein (HDL)
- Polycystic ovary syndrome
- Diabetes mellitus (DM)
- Hypertension (HTN)
- Chronic kidney disease (CKD), stage 3/4
- Family history of coronary artery disease
- Evidence of coronary artery calcification
- Cigarette smoking

- These risk factors, along with other specific criteria, are used to determine a patient's ASCVD risk category, which will determine the patient's goal levels of LDL, Non-HDL and Apolipoprotein B (Apo B). This is shown in the below table:

Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals				
Risk Category	**Risk Factors/Description**	**Treatment Goals$^{\alpha}$ (mg/dL)**		
		LDL	**Non-HDL**	**Apo B**
Extreme	• Progressive ASCVD in patients after achieving an LDL-C <70 mg/dL • Established CV disease in patients with DM, CKD 3/4, or heterozygous familial hypercholesterolemia (HeFH) • History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very High	• Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease • 10-year risk >20% • Diabetes or CKD 3/4 with 1 or more risk factor • HeFH	<70	<100	<80
High	• ≥2 risk factors and 10-year risk 10-20%* • Diabetes or CKD 3/4 with no other risk factors	<100	<130	<90
Moderate	• ≤2 risk factors and 10-year risk <10%*	<100	<130	<90
Low	• 0 risk factors*	<130	<160	NR
**= Subtract 1 risk factor if the person has high HDL, α= Goal for Triglycerides (TG) for all risk categories is <200 mg/dL*				

Treatment Recommendations

- The overall recommendation of the AACE/ACE guidelines regarding pharmacological treatment is that all patients should receive aggressive lipid modifying therapy to achieve the target goals (based on their risk category). This includes recommendations for all major lipid modifying therapies, based on patient characteristics and the outcome desired (below).

AACE/ACE Treatment Recommendations	
Statins	• Recommended as the primary pharmacologic agent to achieve target LDL goals • May be considered to reduce LDL beyond targets for patients in high & very high risk categories
Ezetimibe	• May be considered as monotherapy in reduce LDL and Apo B • Can be used in combination with statins to further reduce LDL and ASCVD risk
PCSK9 Inhibitors	• Should be considered in combination with statins to reduce LDL in patients with familial hypercholesterolemia • May be considered in patients with ASCVD, unable to reach goals with maximally tolerated statin therapy • Should not be used as monotherapy except in statin-intolerant individuals
Omega-3 fatty acids	• 2 to 4 g daily should be used to treat severe hypertriglyceridemia (serum triglycerides >500 mg/dL)
Niacin	• Recommended as an adjunct to reduce serum triglycerides • Should not be used in patients aggressively treated with statins
Fibrates	• Should be used to treat severe hypertriglyceridemia (triglycerides >500 mg/dL) • May improve ASCVD outcomes when TG is ≥200 mg/dL and HDL is <40 mg/dL
Bile Acid Sequestrants	• May be considered to reduce LDL and apo B and modestly increase serum HDL (may increase triglycerides)
Combination Therapy	• Should be considered when the LDL /non-HDL level is markedly increased and monotherapy does not achieve the therapeutic goal

Clinical Practice Guidelines Overview and Summary

- The AACE/ACE Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease provide new guidance on screening, assessment, and treatment for patients with lipid disorders.
- New concepts introduced in the guidelines include support for using measurements of coronary artery calcium scores and inflammatory markers for risk stratification, as well as the creation of an “extreme-risk” category of patients, with a LDL target goal of less than 55 mg/dL.
- In contrast to the 2013 ACC/AHA Cholesterol Guidelines, the AACE/ACE treatment recommendations put an emphasis on treating to achieve targeted LDL goals based on patient characteristics and risk. Because their recommendations are based on achieving these goals, the AACE/ACE guidelines were able to provide recommendations for all lipid lowering therapies and detail the considerations that providers should contemplate when selecting an agent.
- These are the most current clinical practice guidelines available for the management of dyslipidemia at this time, however, updated ACC/AHA guidelines on this topic are expected to be published in 2018.

OVERVIEW OF HEREDITARY ANGIOEDEMA

Introduction

- Hereditary Angioedema (HAE) is a potentially life-threatening, genetic condition that is caused by low blood levels of functioning plasma protein C1 inhibitor (C1-INH). Deficiencies in C1-INH allow unchecked activation of the complement and contact system pathways of the immune system, resulting in recurrent attacks of severe swelling.
- Unlike other forms of angioedema, HAE attacks can be triggered simply by stress, minor trauma or just a simple cold.
- There are three types of HAE, categorized based on blood levels/function of C1-INH:

Type I (80-85% of cases)	**Type II** (15-20% of cases)	**Type III** (undefined % of cases)
▪ Abnormally low levels of normally functioning C1-INH ▪ Treatments outlined in table on page 2	▪ Normal levels of abnormally low functioning C1-INH ▪ Treatments outlined in table on page 2 (same treatment as type I)	▪ HAE with normal C1-INH levels and function ▪ Treatment still being researched but therapies below have been successful

Epidemiology and Symptomology

- HAE is a very rare condition, occurring in an estimated 1 in 10,000-50,000 people in the U.S.
- It is an autosomal dominant condition, with ~75% of patients inheriting the disease from a parent (~25% of cases are caused by a spontaneous mutation in the C1-INH gene at conception).
- The most common symptom of HAE is repeated swelling that can occur anywhere in the body, with over 95% of swelling occurring in the abdomen and skin.
    - The swelling can last for days, change in location and severity over time, and be life-threatening if it occurs in the face, lungs, or throat.
        - Laryngeal swelling is of particular concern, as it carries a mortality rate of up to 30% and occurs in 50% of patients at least once over their lifetime.
- HAE symptoms usually manifest in first or second decade of life, with the average age of onset being 11.2 years.

Bradykinin and HAE

- Deficiencies in C1-INH in patients with HAE and the subsequent unregulated contact system pathway activation results in unchecked production of inflammatory mediators. In terms of HAE symptomology, the most consequential effect of this is an increased production of bradykinin.
- Bradykinin is an inflammatory mediator that, when bound to its receptors in vasculature, causes vasodilation and an increase in vascular permeability.
- While its effects are not intrinsically negative on their own, the unregulated bradykinin production caused by acute attacks in patients with HAE result in a prolongation of its actions, which in turn lead to prolonged and sometime severe inflammation and edema.
- Because of its role, all current drug therapies for treating HAE attacks target this unregulated bradykinin in some fashion.

Treatment and Prophylaxis

- Previously, the only medications used for HAE were anabolic steroids which carried plethora of adverse metabolic and cardiovascular effects.
- In last 10 years, new medications have been approved for the treatment and prophylaxis of HAE attacks that have enabled many patients to effectively treat and manage their HAE without the side effects of anabolic steroids.
- These newer medications fall into two broad categories: C1-INH therapy & non-C1-INH therapies.
    - C1-INH therapies consist of the human derived C1-INH (Berinert, Cinryze, and Haegarda) and recombinant C1-INH (Ruconest).
        - These drugs inhibit the plasma kallikrein, an enzyme that plays an important role in bradykinin synthesis. By preventing the generation of new bradykinin, these drugs are able to reduce or cease further bradykinin-related symptom development during an acute HAE attack.
    - Non-C1INH therapies consist of Kalbitor and Firazyr.
        - Kalbitor is a direct plasma kallikrein inhibitor and therefore achieves its therapeutic effects similar to C1-INH therapies.
        - Firazyr is a bradykinin B2 receptor antagonist that achieves its therapeutic effect by blocking plasma bradykinin from binding to its active site at the B2 receptor in vasculature.
- A table summarizing these agents is below.

FDA-Approved HAE Therapies for Acute Attack Treatment				
Drug	**Category**	**Administration**	**Approved Ages**	**Warnings**
Berinert	Human C1-esterase inhibitor	Intravenous Can be self-administered with training	Adults Pediatrics ≥13 years	Thrombotic Events Anaphylaxis
Ruconest	Recombinant C1-esterase inhibitor	Intravenous Can be self-administered with training	Adults Pediatrics ≥13 years	Thrombotic Events Anaphylaxis
Kalbitor	Kallikrein Inhibitor	Subcutaneous Injection Must be given by a health care provider	Adults Pediatrics ≥12 years	Anaphylaxis Immunogenicity
Firazyr	Bradykinin B2 receptor antagonist	Subcutaneous Injection Can be self-administered with training	Adults	May worsen acute ischemia Immunogenicity

FDA-Approved HAE Therapies for Attack Prophylaxis				
Cinryze	Human C1-esterase inhibitor	IV administration. Can be self- administered with training	Adults Pediatrics ≥13 years	Thrombotic Events Anaphylaxis
Haegarda	Human C1-esterase inhibitor	Subcutaneous Injection Can be self- administered with training	Adults Pediatrics ≥13 years	Thrombotic Events Anaphylaxis

- **Final points on HAE treatment:**
  - HAE Attack Prophylaxis: The US Hereditary Angioedema Association Medical Advisory Board recommends that the decision to use these agents should only be made after taking into account multiple patient characteristics such as attack frequency and severity, comorbid conditions, patient access to emergent treatment, and patient experience and preference.
    - All patients should be reviewed for whether there is a need for attack prophylaxis regularly, as HAE severity waxes and wanes over time.
  - Patient Education: Because of the potentially high mortality risk of HAE attacks, all patients being treated for HAE should be well educated on the need for having a management plan for acute attacks that is known by the patient and their caregiver(s).
    - The plan should include the patient having access to 2 doses of on-demand treatment at all times.
    - Patients receiving on-demand treatment that is approved for self-administration (Berinert, Ruconest, and Firazyr), as well as their caregiver(s), should be fully trained on how to administer the medication.

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