Letters to the Editor

Importance of Dyslipidemia Screening in Children and Adolescents

Original Article: Right Care for Children: Top Five Do's and Don'ts

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To the Editor: Familial hypercholesterolemia (FH) is present in approximately one out of 250 children, resulting in lifelong elevated cholesterol and premature coronary artery disease (CAD). FH triples the likelihood of CAD at any given low-density lipoprotein cholesterol (LDL-C) level. FH can be easily identified in childhood by simple lipid screening.[1-5] Some guidelines recommend universal lipid screening in children and adolescents nine to 11 years and 17 to 21 years.[1,2,4]

In this article by Dr. Schefft and colleagues, routine testing for dyslipidemia in children and adolescents is listed as a top five "don't" for the right care for children, implying that physicians screening for dyslipidemia are providing the wrong care. The safety of statin therapy in children is also questioned. This statement contradicts the 2016 U.S. Preventive Services Task Force report, which acknowledges the importance of early detection of FH and multifactorial dyslipidemias, leaving the decision about screening to clinical judgment, despite evidence that cholesterol screening in childhood is insufficient to assess the balance of benefits and harms.[5]

Many levels of evidence support screening and early treatment of severe hypercholesterolemia, including FH. There is a significant linear relationship between cholesterol-years of exposure and the risk of future CAD. For every mmol per L (38 mg per dL) of lifelong genetically elevated LDL-C, the risk of CAD is increased by 50%. FH-associated mutation triples the risk of CAD at any level of cholesterol. Lowering LDL-C early in life can alter this relationship. FH registry studies and meta-analyses of randomized trials demonstrate that patients with the highest cholesterol levels who are treated early benefit the most from treatment, with as much as a 75% risk reduction in event rates in young patients with FH.[1-3]

There are no published studies suggesting harm from statin treatment, and there are no data reports of adverse events in children. Current data actually suggest that statins may be better tolerated when prescribed at younger ages.[1,2,4,5]

Family physicians are uniquely positioned to screen for, detect, and treat prevalent genetic conditions such as FH that affect families across many generations. Similar to monogenic causes of cancer, FH has a Tier 1 recommendation for testing of first-degree relatives of affected patients issued by the Centers for Disease Control and Prevention.[2] Lipid screening should be one of the "do's" of right care for children, not one of the "don'ts."

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Author disclosure: Dr. Gidding is the medical director of the FH Foundation. He receives research funding from the National Institute of Diabetes and Digestive and Kidney Diseases as a consultant for the TODAY studies. He was a coauthor of the 2011 National Heart, Lung, and Blood Institute Cardiovascular Risk Reduction in Childhood and Adolescence guideline. Dr. Wójcik has no relevant financial affiliations.

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In Reply: We appreciate the thoughtful response by Drs. Wójcik and Gidding to our article and thank them for their numerous contributions surrounding the management of familial hypercholesterolemia (FH). We agree that early diagnosis and initiation of lipid-lowering medications for children with FH are important for their longevity and quality of life. As the authors state, the U.S. Preventive Services Task Force chose not to recommend for or against routine lipid screening in children, a position supported by the American Academy of Family Physicians.[1] The National Heart, Lung, and Blood Institute (NHLBI) panel's basis for universal screening is the suggestion that obtaining family history is insensitive for the detection of children at high risk of FH. However, the studies cited to support this concern used family history as a screen for high lipid levels, not FH. The LDL-C thresholds used in these studies were surprisingly low (some as low as 135 mg per dL [3.50 mmol per L]).[2] Therefore, an otherwise healthy nine year old with no family history of cardiovascular disease and a borderline elevated LDL level would theoretically be "missed." An estimated 200,000 children and adolescents could qualify for statin therapy if universal screening was widely implemented.[3]

Although existing data suggest a low rate of adverse events, the long-term consequences of lipid-lowering medications for children are a significant concern. The data supporting the safety of statins in children are almost entirely industry sponsored, short in time horizon, and exclusively in children with FH.[4] The safety and effectiveness of statins in the population most impacted by universal screening, otherwise healthy children with common comorbidities such as obesity, have not been studied. Additionally, there is evidence that cholesterol levels among adolescents have decreased over time without screening or treatment.[5]

Half of the NHLBI expert panel had conflicts of interest related to 16 pharmaceutical and biotechnology companies.[6] We recognize the important role that the pharmaceutical industry plays in bringing innovative medications to market; however, the potential for these relationships to influence guideline development cannot be ignored.

Under the premise that "do no harm" should be the fundamental starting point in health care, we disagree that universal lipid screening should be considered a top five "do" for the right care for children. Although identifying and treating patients with FH are important, the net benefits of screening all children, especially children without a family history of cardiovascular disease, are uncertain. We hope that research in this area continues to better inform clinical decision-making.

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Progestin Therapy Not Likely to Be Harmful in Women with First Trimester Bleeding

Original Article: First Trimester Bleeding: Evaluation and Management

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To the Editor: The authors of this article provided a comprehensive and valuable overview of caring for patients with first trimester bleeding. However, we disagree with their conclusions on the role of progestins in the management of threatened abortion and the prevention of early pregnancy loss.

They state that "bed rest or progestins should not be recommended to prevent early pregnancy loss in patients with first trimester bleeding because these interventions have not been proven effective." However, evidence of no benefit (bed rest[1]) is a different problem than no evidence of benefit (progestins, until recently). The Cochrane review cited in the article was

updated in August 2018 and reported that the use of a progestogen probably reduces the rate of spontaneous miscarriage, which was supported by moderate-quality evidence.[2]

The authors also state that "there is insufficient evidence to support the use of progestin for the prevention of early pregnancy loss," citing the Cochrane review and a practice bulletin from the American College of Obstetricians and Gynecologists, which cites the same Cochrane review. However, a separate Cochrane review concluded that for women with unexplained recurrent miscarriages, progestogen therapy probably reduces the rate of miscarriage in subsequent pregnancies.[3] A draft guideline of the United Kingdom's National Institute for Health and Care Excellence suggests that progestin therapy be considered, but that patients be counseled that the evidence of benefit is not strong.[4]

There is a need for high-quality studies to determine the optimal dosage and route of administration in a population representative of patients we treat. In the meantime, offering progestin therapy to patients in this difficult situation is an option that is not likely to be harmful and may very well be helpful.

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In Reply: We thank Drs. Bryce and Sisk for highlighting this new evidence, which was published after the final submission of our article. We agree with the conclusions they share from the updated Cochrane reviews regarding the potential benefits of progestin therapy in threatened miscarriage and the prevention of recurrent miscarriage.[1,2] We appreciate their mention of proposed guideline updates and expect that other national organizations may issue updates as well. We also strongly support their suggestion that more high-quality research is needed regarding optimal dosing and route of administration of progestins and to clarify the magnitude of the benefits vs. harms.

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Corrections

Updated Guideline and Terminology. The article, "Testosterone Therapy: Review of Clinical Applications" (October 1, 2017, p. 441) included a section titled, "Testosterone Therapy in Female-to-Male Transgender Patients" beginning on page 447, which was based on information from a 2009 Endocrine Society clinical guideline. At the time this article was written, an updated version of this guideline from 2017 was available but was overlooked by the authors. Based on information in the 2017 guideline, the text for this section of the article has been rewritten by the authors and some of the terminology was updated. The section title was also retitled "Testosterone Therapy in Transgender and Gender Diverse Patients." The revised text reads as follows: "Testosterone therapy may also be used to facilitate gender transition for transgender men and gender nonbinary individuals desiring masculinization. Primary care physicians are increasingly involved in the initiation and management of testosterone therapy for this population. Although a full discussion of the use of testosterone for the treatment of gender incongruence is beyond the scope of this article, physicians can find concise guidelines in the 2017 Endocrine Society publication, "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," at https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines/gender-dysphoria-gender-incongruence.[66]" Reference 66 was also replaced with the citation for the updated guideline: Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2017;102(11):3869-3903. The online version of the article has been corrected. ■