Lipid Screening and Treatment Recommendations for Children and Adolescents

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Atherosclerotic lesions begin in childhood, and the presence and progression of those lesions are associated with cardiovascular disease risk factors, including lipid dyslipidemias.

The early identification and treatment of youth with cardiovascular disease (CVD) risk factors and dyslipidemias can alter the atherosclerotic process. The increasing incidence and prevalence of overweight and obesity in youth and the failure of targeted screening strategies, suggest universal lipid screening is necessary. Universal screening is recommended by recent NIH guidelines as part of a comprehensive approach to reducing atherosclerotic risk for youth. Screening goals include the identification of youth with abnormal lipid levels and/or inherited lipid disorders in order to focus lifestyle and treatment recommendations on those at highest risk for early CVD.
The primary treatment for most children and adolescents with dyslipidemias is lifestyle change, including a diet low in total and saturated fat and cholesterol with appropriate calories for normal growth and development, weight control, and regular physical activity. Children with familial dyslipidemias, obesity, metabolic syndrome, and other medical problems which increase atherosclerotic risk, may also be candidates for pharmacologic therapy. The indications for lipid screening and for management, including use of medication for children with significant dyslipidemias, are reviewed.

ATHEROSCLEROSIS

Atherosclerosis begins in childhood and has been shown to be related directly to the presence and intensity of CVD risk factors, including elevated LDL-cholesterol, non-HDL-C, apolipoprotein B, triglycerides, and low levels of HDL-cholesterol.1-4

Longitudinal cohort studies demonstrate that atherosclerotic lesions in children and adolescents, including fatty streaks and fibrous plaques, are significantly related to lipoprotein levels and to other CVD risk factors.2,4 Abnormal levels of lipids and lipoproteins are associated with accelerated development of atherosclerosis shown at autopsy,2,4 and in imaging studies evaluating subclinical atherosclerosis, including endothelial dysfunction, increased carotid intimal media thickness (CIMT), and presence of coronary artery calcium.5,6

In young adults with elevated LDL-cholesterol (LDL-C), there is convincing evidence that lipid-lowering therapy with statins significantly decreases the incidence of major coronary and cerebrovascular events.9 However, the screening and treatment of children for cholesterol disorders remains controversial because there are no studies showing that identifying and treating dyslipidemias in children and adolescents will reduce CVD events in later life. Long-term randomized controlled trials of screening and treatment for youth are not feasible due to the length of the required study, large required sample sizes, and prohibitive costs as well as the ethical dilemma of withholding evidence-based care once subjects reached young adulthood.9

In the past 2 decades, there has been a major increase in the prevalence of overweight and obesity, which has increased the number of children with dyslipidemia.10 Previous pediatric cholesterol guidelines focused on the identification of children with elevated LDL-C or familial hypercholesterolemia (FH). However, due to the high prevalence of overweight and obese children and adolescents, the most common dyslipidemia in youth is now a combined pattern with moderate to severe elevation in triglycerides (TG), normal to mildly elevated LDL-C, and reduced HDL-C. Both dyslipidemic patterns have been shown to be associated with initiation and progression of atherosclerotic lesions in children and adolescents.1,11

There is good evidence that optimizing potential risk factors in childhood can delay the development and progression of the atherosclerotic process. From autopsy and longitudinal cohort studies, it has been shown that those who enter adult life without identified CV risk factors have minimal atherosclerosis at age 30 to 34 years, absence of subclinical atherosclerosis as young adults, extended life expectancy, and a better quality of life free from CVD.12,13 Healthy male children randomly assigned to a low saturated fat, low cholesterol diet from the age of 7 months to 11 years had significantly lower total and LDL-C levels throughout childhood than control children. At age 11 years, the low saturated fat group had enhanced vascular endothelial function compared with controls.14 High-risk children with severe elevation of LDL-C treated effectively with medication have less carotid atherosclerosis than untreated controls, and this effect is enhanced when lipid-lowering therapy is started at younger ages.15,16

Due to the increasing presence of dyslipidemia in the US population, demonstrated atherosclerosis associated with dyslipidemias, and evidence for safety and efficacy of treatment, it is now recommended that all children undergo lipid screening in childhood. Treatment, including lifestyle changes and medication, are indicated for children and adolescents whose lipid levels place them at high risk for accelerated atherosclerosis and early CVD.1

DEFINITION AND TYPES OF DYSLIPIDEMIA

Dyslipidemias are abnormal levels of lipids and lipoproteins, and are influenced by both genetics and environmental factors (nutrition, activity, social factors, and more).1,11 Dyslipidemias are defined by reference to normal lipid levels for age, gender, and race based on population distributions and genetic disorders. Dyslipidemias can also be due to secondary causes, most importantly, obesity.

The genetic lipid disorders may be the result of a single gene defect or of polygenic defects that lead to abnormal lipoprotein metabolism.1 The most common disorders are familial heterozygous hypercholesterolemia (FH) and familial combined hyperlipidemia (FCH). Heterozygous FH occurs at a frequency of one in 500 in the US population and

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The primary treatment for most children and adolescents with dyslipidemias is lifestyle change.
presents with severe elevation in total and LDL-C present from birth. FH is associated with premature CV disease, with 25% of females and 50% of males experiencing CVD events by age 40 years.\textsuperscript{11}

In childhood, FCH is almost always associated with overweight or obesity and presents with moderate to severe elevation in TG, normal or mildly elevated LDL-C, and reduced HDL-C; small, dense LDL particles are also often present. This dyslipidemia pattern is also often associated with insulin resistance/glucose intolerance and hypertension as the metabolic syndrome.\textsuperscript{10,11,17,18}

Polycystic ovary syndrome is another metabolic abnormality associated with insulin resistance and the pattern of combined dyslipidemia, accelerated by weight gain in female adolescents. Low HDL-C is also associated with premature CVD.\textsuperscript{7} HDL can be reduced significantly due to overweight/obesity, sedentary lifestyle, tobacco use, hypertriglyceridemia, or inherited forms of low HDL production or catabolism.\textsuperscript{11}

**NORMAL LIPID LEVELS FOR CHILDREN AND ADOLESCENTS**

The normal and reference values for cholesterol are based on the results of population screening, with defined age- and gender-specific levels shown in Table 1.\textsuperscript{1,19-21} Defining the 50th percentile as borderline-high, and the 75th percentile as “high cholesterol” is recommended based on population and pathological research but for clinical purposes, values above the 75th percentile are described as borderline-high and above the 95th percentile as high.\textsuperscript{22}

Longitudinal studies that have followed children from early childhood into adult life demonstrate strong statistical tracking for lipid levels.\textsuperscript{23,24} Using the 95th percentile as abnormal, total cholesterol (TC) levels have 50% to 69% sensitivity and 90% to 98% specificity in accurately assessing LDL-C elevations in adult life. Approximately 50% of children with elevated TC and LDL-C will have elevated lipid levels as adults, more than twice that predicted, with a much higher proportion of children with lipid levels at or above the 95th percentile remaining high as adults.\textsuperscript{23,24} Importantly, total and LDL-C levels decrease on average 10% to 20% during adolescence, more for boys than girls, but steadily increase again after adolescence.\textsuperscript{11,25} HDL-C levels in males also decrease after puberty.\textsuperscript{25} Pubertal changes cause sensitivities and specificities to be lowest at age 14 to 16 years, regardless of lipid status.\textsuperscript{11}

**SCREENING AND ASSESSMENT OF RISK AND LIPID DISORDER**

Recommended screening guidelines for children and adolescents are presented in Table 2. In the original National Cholesterol Education Program guidelines from the National Heart, Lung, and Blood Institute published in 1992, lipid screening in children was based on the presence of a positive family history of early coronary disease or of abnormal lipids. Since that time, it has been shown that using family history as a primary factor for screening children will miss the majority of children with inherited dyslipidemias, primarily because family history questions are not standardized and have limited diagnostic accuracy, sensitivity, and specificity.\textsuperscript{9}

The previously recommended screening strategies have low adherence rates by providers and parents of at-risk children. When an accurate family history of premature CVD is present, there is a higher risk that the progeny will have abnormal lipid levels.\textsuperscript{26-28} Although overweight is the best predictor of known risk factors for dyslipidemia, the effects are variable.\textsuperscript{17,18,29,30} The presence of multiple risk factors has not been adequately evaluated to assess the ability to predict a child with dyslipidemia.

Based on the current evidence review,\textsuperscript{1,11} the new guidelines recommend universal screening as the approach that will best identify children and adolescents with risk for premature atherosclerosis due to abnormal lipid values, as outlined in Table 2. The NHLBI panel recommends that at age 10 years, all children be screened for dyslipidemia. This is an age when children are able to fast consciously, the values are predictive of future adult lipoprotein profiles, and children may be more cooperative regarding lifestyle change than during adolescence.\textsuperscript{1} Also, since total and LDL-C levels decrease 10% to 20% or more during adolescence, it is preferable to screen children at risk for inherited dyslipidemias before adolescence. If normal at age 10 years, lipid levels should be repeated at approximately 18 years of age, when results are most predictive of what they will be in the next 2 decades. If abnormal, the algorithms in Figures 1 and 2 indicate appropriate management using lifestyle change and medication based on the degree of lipid abnormality.\textsuperscript{1}

In specific high-risk situations, lipid testing is recommended on an individual basis, such as in children with diseases associated with dyslipidemia or those in high-risk families with known dyslipidemia or premature CVD as outlined in Sidebars 1 and 2. The presence of obesity and other conditions known to be associated with dyslipidemia, such as diabetes, nephrotic syndrome, etc, indicate the need for a higher frequency of testing. At a minimum, children with these conditions should be screened for dyslipidemia with diagnosis of these conditions, and then again every 5 years subsequently.\textsuperscript{1}

In the past, TC levels have been chosen as the initial screening test by most health care organizations and guidelines. The new guidelines recommend screening with non-HDL-C, a value that is calculated from nonfasting total cholesterol and HDL-C: Non-HDL-C = TC– HDL-C.
# TABLE 1.
## Evidence-Based Recommendations for Lipid Assessment

<table>
<thead>
<tr>
<th>Age</th>
<th>Screening</th>
<th>Grade*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 2 years</td>
<td>No lipid screening</td>
<td>C</td>
</tr>
<tr>
<td>2-8 years</td>
<td>No routine lipid screening</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Measure fasting lipid profile x 2, average results if:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Parent, grandparent, aunt/uncle or sibling with MI, angina, stroke, CABG/stent/ angioplasty at &lt; 55 y in male, &lt; 65 y in female</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Parent with TC ≥ 240 mg/dL or known dyslipidemia</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Child has diabetes, hypertension, BMI ≥ 95th percentile or smokes cigarettes</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Child has a moderate or high risk medical condition (see Sidebar 1)</td>
<td>B</td>
</tr>
<tr>
<td>9-11 years</td>
<td>Universal Screening</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Non-fasting lipid profile:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Calculate non–HDL-C: Non–HDL-C = TC - HDL-C</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-HDL ≥ 145 mg/dL, HDL &lt; 40 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ Fasting lipid profile x 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fasting lipid profile:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDL-C ≥ 130 mg/dL, non–HDL-C ≥ 145 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HDL-C &lt; 40 mg/dL, TG ≥ 100 mg/dL if &lt; 10 y,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 130 mg/dL if ≥ 10 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ Repeat fasting lipid profile, average results.</td>
<td></td>
</tr>
<tr>
<td>12-16 years</td>
<td>Universal screening once in this time period:</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Non-fasting lipid profile:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Calculate non–HDL-C: Non–HDL-C = TC - HDL-C</strong></td>
<td></td>
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<td></td>
<td>Non-HDL ≥ 145 mg/dL, HDL &lt; 40 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ Fasting lipid profile x 2</td>
<td></td>
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<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fasting lipid profile:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17-19 y: non–HDL-C ≥ 145 mg/dL, HDL-C &lt; 40 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ Fasting lipid profile x 2</td>
<td></td>
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<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-21 y: Non–HDL-C ≥ 190 mg/dL, HDL-C &lt; 40 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ Fasting lipid profile x 2, average results</td>
<td></td>
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<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasting lipid profile:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDL-C &gt; 130 mg/dL, non–HDL-C &gt; 145 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HDL-C &lt; 40 mg/dL, TG &gt; 130 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ Repeat fasting lipid profile, average results</td>
<td></td>
</tr>
</tbody>
</table>

*ATP = Adult Treatment Panel; BMI = body mass index; CABG—coronary artery bypass graft; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TC = total cholesterol; TG = triglycerides.

*Grades reflect the findings of the evidence review.

RISKS ASSOCIATED WITH SCREENING

No studies have identified any harm from screening for cholesterol in children and adolescents. A concern is whether screening abnormalities may cause labeling of children whose elevated lipid levels do not track into adulthood, although evidence is not sufficient to show any concern. There is a significant rate of noncompliance with screening and follow-up recommendations by both clinicians and parents of children with abnormal levels. A number of factors have been suggested, including inconvenience, discomfort with the screening tests, refusal by the child or parent, concerns about upsetting the child, and resistance regarding dietary and lifestyle changes, among others. The absence of harm and the benefits of preventing the development of atherosclerosis is justification for attention to CVD risk factor screening and control in youth.

TREATMENT OF DYSLIPIDEMIA

Identifying a child as having abnormal lipid levels should change management by the clinician. Dietary recommendations that will optimize CV risk for all children are outlined in the previously published section on nutrition and diet. Specific dietary changes are recommended as the first step for any child with LDL-C or TG greater than the 95th percentile, provided at: www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. Behavioral approaches, in addition to dietary changes, including engaging the family by a registered dietitian, are the most effective approach for dietary change.

<table>
<thead>
<tr>
<th>Category</th>
<th>Acceptable (mg/dL)</th>
<th>Borderline High (mg/dL)</th>
<th>High (mg/dL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt; 170</td>
<td>170-199</td>
<td>&gt; 200</td>
</tr>
<tr>
<td>LDL-C</td>
<td>&lt; 110</td>
<td>110-129</td>
<td>&gt; 130</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>&lt; 120</td>
<td>120-144</td>
<td>&gt; 145</td>
</tr>
<tr>
<td>ApoB</td>
<td>&lt; 90</td>
<td>90-109</td>
<td>110</td>
</tr>
<tr>
<td>TG</td>
<td>0-9 years &lt; 75</td>
<td>75-99</td>
<td>&gt; 100</td>
</tr>
<tr>
<td></td>
<td>10-19 years &lt; 90</td>
<td>90-129</td>
<td>&gt; 130</td>
</tr>
<tr>
<td>Category</td>
<td>Acceptable (mg/dL)</td>
<td>Borderline High (mg/dL)</td>
<td>Low (mg/dL)*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&gt; 45</td>
<td>40-45</td>
<td>&lt; 40</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>&gt; 120</td>
<td>115-120</td>
<td>&lt; 115</td>
</tr>
</tbody>
</table>

ApoA-I = apolipoprotein A-I; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

*The cutpoints for high and borderline high represent approximately the 95th and 75th percentiles, respectively. Low cutpoints for HDL-C and apoA-I represent approximately the 10th percentile.

Source: McBride PE, Kavey RW.
Figure 1. Management of high LDL cholesterol in children.

* Use of drug therapy is limited to children >10 years with defined risk profiles.
† In a child with LDL-C > 190 mg/dL, and other RFs, trial of CHILD 2-LDL may be abbreviated.
‡ In consultation with a lipid specialist.
CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; RF = risk factor; TG = triglyceride.
Children with dyslipidemias should have a detailed family history taken and assessment for causes of hyperlipidemia and additional risk factors or risk conditions before considering medication. Decisions to treat should be considered in the context of overall CVD risk and based on family and patient preferences. Optimal treatment of the secondary causes of dyslipidemias and associated high-risk conditions is vital before considering treatment. Based on population data, if universal screening was implemented, less than 1% of adolescents would be potentially eligible for pharmacologic treatment because of elevated LDL-C.

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tiple statin trials in children with treatment duration ranging from 4 months to 5 years.\textsuperscript{1,41} No significant safety issues occurred, including adverse events, abnormal sexual development, or muscle or liver toxicity.\textsuperscript{1,41} Statin therapy is recommended for first-line pharmacologic therapy for patients with persistent severe elevation of LDL-C levels (Figure 1). Statins reduce endogenous cholesterol production and cause an upregulation of LDL receptors, significantly reducing LDL-C and VLDL cholesterol. Statin trials have not demonstrated any impact on growth or development, nor any cognitive impairment, for children and adolescents. Statins may interact with other medications, so appropriate consideration is advised. The lowest starting dose is recommended for youth, and doses may be increased if there is an inadequate response in 1 to 3 months. No significant safety issues associated with increasing statin doses have been demonstrated to date in children.\textsuperscript{1,41} Recognized statin side effects include myositis and hepatitis. These side effects are rare in children, may be reduced by lowering the statin doses, and are reversible if the medication is stopped. The statin medications are shown in detail in the guidelines.\textsuperscript{1}

**Bile Acid Resins**

Bile acid resins bind and reduce enterohepatic circulation of bile salts in the intestinal lumen, causing reduced bile salts and cholesterol in the liver. This decrease signals for increased production of LDL-C receptors and increased clearance of circulating LDL-C. Bile acid resins may cause bloating, nausea, and stool changes, which limit patient acceptance or adherence, and this is dose-dependent. Bile acid resins may reduce serum levels of vitamins A, D, E, and K, and may interfere with the absorption of some other medications. Bile acid resins are particularly effective in combination with a statin to low-

### SIDEBAR 1.

**Special Risk Conditions for Dyslipidemia in Children**

**High Risk**
- Diabetes mellitus, type 1 and type 2
- Chronic renal disease/end-stage renal disease/post-renal transplant
- Post-orthotopic heart transplant
- Kawasaki disease with current aneurysms

**Moderate risk**
- Kawasaki disease with regressed coronary aneurysms
- Chronic inflammatory disease (systemic lupus erythematosus, juvenile rheumatoid arthritis)
- Human immunodeficiency virus infection (HIV)
- Nephrotic syndrome

Source: McBride PE, Kavey RW

### SIDEBAR 2.

**Risk Factor Definitions for Dyslipidemia Algorithms**

**Positive Family History**
- Myocardial infarction, angina, coronary artery bypass graft/stent/angioplasty, sudden cardiac death before age 55 years in parent, grandparent, aunt or uncle; male < 55 years, female < 65 years

**High-Level Risk Factors**
- Hypertension requiring drug therapy (BP ≥ 99th percentile ± 5 mm Hg)
- Current cigarette smoker
- BMI ≥ 97th percentile
- Presence of high-risk conditions (diabetes mellitus is also a high-level risk factor but it is classified here as a high-risk factor to correspond with Adult Treatment Panel III recommendations for adults that diabetes mellitus be considered a cardiovascular disease equivalent)

**Moderate-Level Risk Factors**
- Hypertension not requiring drug therapy
- BMI ≥ 95th percentile, < 97th percentile
- HDL-C < 40 mg/dL
- Presence of moderate-risk conditions

**BMI** = body mass index; **BP** = blood pressure; **HDL-C** = high-density lipoprotein cholesterol.

Source: McBride PE, Kavey RW
Ezetimibe

Ezetimibe lowers LDL-C levels by reducing intestinal cholesterol absorption and upregulating LDL-C receptors. Minimal data is available for the use of ezetimibe for children, although small studies demonstrate safety and effectiveness. Ezetimibe may significantly elevate hepatic transaminase levels, especially with combination therapy. There is currently no FDA approval for the use of ezetimibe in children. The LDL-C level and timing suggested for using medication is provided in the algorithm (Figure 1).

Lifestyle Modification

For children with high TG and/or low HDL-C, healthy lifestyle and optimal body weight are the most important treatment recommendations. Patients with high TGs often have very low HDL-C levels and when TG levels are lowered, HDL-C levels usually rise. For those with associated HDL-C and TG abnormalities that have not normalized with lifestyle change, therapy with fibrates or fish oil could be considered under the direction of a lipid expert. Omega-3 fish oil supplements are very effective in lowering TG levels in adults and in small series in children. Fibrates are safe and effective for adults with elevated TG and a small series demonstrated safety and effectiveness in children. There is limited research on the use of niacin for dyslipidemic children, with a single study indicating a high rate of side effects. Consultation with a pediatric lipid specialist is recommended before considering the use of fibrates, niacin, or combination therapy for youth. Children with sustained TG levels of at least 500 mg/dL may have an underlying genetic defect and require immediate intervention because of the risk for pancreatitis. A very low-fat diet is recommended (<10%-15% fat), medications are usually required, and consultation with a qualified pediatric dietician and a lipid specialist is recommended. These children may require the use of medium-chain TGs in their diet; this can significantly lower TG serum levels.

The recommended cholesterol cutpoints for the use of medication and age-specific recommendations for the pharmacologic management of dyslipidemia are shown in Figures 1 and 2. Specific medication information is available in the guidelines, accessible at: www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm.

CONCLUSION

An extensive evidence review led to the new NHLBI recommendations for screening and treatment of dyslipidemia in children and adolescents. Here, we have provided a summary of the most important evidence and the related recommendations for detection and management. The full report of the guidelines provides the complete evidence and detailed age-specific recommendations to guide pediatric care providers in providing optimal care for children with dyslipidemia.

REFERENCES

17. Gidding SS, Bao W, Srinivasan SR, Berenson GS. Effects of secular trends in obesity on


