Patterns of Lipid Lowering Therapy among Children Ages 8-20 Years

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Objectives Pediatric guidelines in 2008 and 2011 recommended lipid lowering therapy in children ≥8 years of age with high-risk cardiovascular conditions, such as familial hypercholesterolemia (FH). Our objective was to describe the patterns and predictors of lipid lowering therapy initiation in commercially insured children between 2005 and 2010.

Study design Using commercial health plan data on children ages 8-20 years from 2004-2010, we estimated rates of lipid lowering therapy initiation overall and stratified by age. Using a nested case-control design, we used multivariable logistic regression to identify temporal, demographic, clinical, and health utilization characteristics associated with lipid lowering therapy initiation.

Results Among >13 million children, 665 initiated lipid lowering therapy for an incidence rate 2.6/100 000 person-years (PY). Incidence rates were highest in 2005 (4.1/100 000 PY) and 2008 (3.9/100 000 PY), with no discernable secular trend. Rates of lipid lowering therapy initiation were significantly greater in children ≥15 years of age (OR 2.9 [95% CI 5.2-13.0]), males (2.1 [1.7-2.4]), and those with a diagnosis of FH (165.2 [129.0-211.6]), other dyslipidemia (175.5 [143.2-215.3]), diabetes type I (7.7 [4.7-12.4]), diabetes type II (13.6 [8.5-21.7]), hypertension (8.1 [4.9-13.3]), obesity (7.8 [4.7-12.7]), and ≥5 outpatient visits (1.5 [1.2-1.7]), and children with dispensing of ≥2 nonlipid lowering therapy prescriptions were less likely to initiate lipid lowering therapy (0.2 [0.2-0.3]).

Conclusions Despite new guidelines, lipid lowering therapy initiation in children is low and has not increased through 2010. Although diagnosis of FH and other dyslipidemias was associated with higher probability of lipid lowering therapy initiation, our findings suggest lipid lowering therapy is underutilized in this population given the prevalence of these disorders. *(J Pediatr 2015;167:113-9)*.

Pathologic and epidemiologic data demonstrate that atherosclerosis begins at a young age and that early treatment can reduce precursors to cardiovascular disease (CVD) later in life.[1-4] Multiple observational studies and clinical trials have demonstrated the efficacy of pharmacologic lipid lowering therapy in reducing markers of CVD.[5-12] The majority of pediatric studies have focused on children with familial hypercholesterolemia (FH), a dominant negative genetic condition characterized by significantly elevated low-density lipoprotein cholesterol levels starting at birth. It is well recognized that children with FH are at a substantially higher risk for coronary events earlier in adulthood and exhibit precursors to CVD in late adolescence and young adulthood. Although lifestyle modification alone is insufficient as a means of risk reduction, pharmacotherapy appears to be of benefit.[13,14]

As a result of the growing evidence to support early intervention, in 2008 the American Academy of Pediatrics (AAP) released a policy statement on "Lipid Health and Cardiovascular Screening in Childhood," updating the 1998 policy statement "Cholesterol in Childhood"[15] to include pharmacologic treatment with statins of children 8 years and older—pravastatin exclusively for children 8-10, and all statins for children 10 and older—who are the highest at risk for CVD.[1] The 2008 report was followed in 2011 by a report from an expert panel commissioned by the National Heart, Lung, and Blood Institute (NHLBI) and endorsed by the AAP, recommending similar treatment guidelines with the exception that the minimum age recommended for initiation of lipid lowering therapy was 10 years.[16] Both sets of guidelines were met with controversy when released. Critics argued that the guidelines promoted medicating children without sufficient evidence on the long-term safety of lipid lowering therapy use and warned of an "epidemic" of pharmacologic treatment in children.[17]

Prior to the release of the AAP and NHLBI guidelines, estimates of the prevalence of statin use in children under the age of 18 years, both privately insured and Medicaid recipients, was between 0.0112%[18] and 0.0168%.[19] Both estimates

AAP	American Academy of Pediatrics
CVD	Cardiovascular disease
FH	Familial hypercholesterolemia
ICD-9	*International Classification of Diseases, Ninth Revision*
NHLBI	National Heart, Lung, and Blood Institute
PY	Person-years

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N.J. was supported by the American Heart Association-Founders Affiliate (13PRE16270004); she worked as a Global Health and Economics Outcome Research fellow for Pfizer, Inc in a capacity unrelated to the report. J.Z. was supported by the National Heart, Lung, and Blood Institute (K23 award- HL111335). D.D. is a full-time employee of Optum Epidemiology; he conducted this work while a full-time employee of Brown University, during which he was a paid consultant to Optum Epidemiology. J.N. is supported by Bristol-Myer-Squibb; she has consulted for Bristol-Myer-Squibb and Janssen Pharmaceutical on topics unrelated to this report. G.W. and J.Z. declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.04.004

are from studies using the CVS Caremark dispensing database, are limited to 2004 and 2007, and lack data on clinical covariates.

The primary objective of this study was to describe the patterns of, and clinical variables associated with, lipid lowering therapy initiation in a commercially insured population of children aged 8-20 years between 2005 and 2010, thereby spanning the 2008 lipid management guidelines. We hypothesized that the rate of lipid lowering therapy initiation would increase over time and that older children and children with multiple comorbidities would be more likely to receive lipid lowering therapy. We further hypothesized that the presence of certain comorbidities might cause physicians to be more aggressive with screening for dyslipidemias or more likely to treat children for such dyslipidemias. Because of the particular focus on children with genetic dyslipidemias included in the 2008 AAP guidelines, a secondary objective was to investigate factors associated with initiation of lipid lowering therapy among commercially insured children with a diagnosis of FH or other dyslipidemia.

Methods

Data on demographic characteristics, pharmacy claims, and clinical diagnoses were extracted from the Truven Health Analytics MarketScan databases (Truven Health Analytics, Ann Arbor, Michigan) for calendar years 2004 through 2010. All data were de-identified, and did not require approval of the institutional review board. The MarketScan database includes claims data on employees and their dependents from employers and health insurers. The enrollment database was used to assess eligibility, and clinical information was collected from the inpatient and outpatient claims databases. Uses of lipid lowering therapy were collected from the outpatient pharmacy claims database and included all uses of a statin, niacin, ezetimibe, fibric acid derivative, or bile acid sequestrant.

The primary outcome of the study was incident lipid lowering therapy, defined as dispensing at least 1 lipid lowering agent following a period of 12 consecutive months of no recorded use. We used measures of incidence instead of prevalence in order to capture changes in the decision to initiate lipid lowering therapy, as prevalence measure can reflect changes in discontinuation of lipid lowering therapy and differential right censoring. Patients aged 8-20 years between 2005 and 2010 with at least 12 months of continuous enrollment in a health plan were eligible for inclusion in the analysis. Follow-up time at-risk of lipid lowering therapy initiation began on the first day after the 12 months of continuous enrollment, therefore, estimates of lipid lowering therapy initiation begin in 2005. For our analysis, we assessed the presence of the age and sex as well as clinical diagnoses identified as risk factors for CVD in the consensus statement endorsed by the AAP "Cardiovascular Risk Reduction in High-Risk Pediatric Patients"[20] using the following *International Classification of Diseases, Ninth Revision* (ICD-9) codes: FH (272.0) and other dyslipidemia (270.1-270.9), hypertension (401.xx-404.xx, 796.0, 796.2), diabetes mellitus types I (252.x1, 252.x3) and II (252.x0, 252.x2), obesity (278.xx), congenital heart disease (746), chronic kidney disease/end stage renal disease (585), Kawasaki disease (446.1), and heart transplant (V42.1, 996.83) and chronic inflammatory diseases (375.1, 375.3). FH was defined using the ICD-9 code 272.0, however, because this code also includes Fredrickson type IIa hyper hyperlipoproteinemia, hyperbetalipoproteinemia, hyperlipidemia group A, and low-density-lipid hyperlipoproteinemia, we cannot be certain that this diagnosis is meant to specifically refer to FH. As such, patients with an ICD-9 code for 272.0 are presumed, but not confirmed, to have FH. A clinical diagnosis was deemed present when identified on at least 2 outpatient or 1 inpatient claims within the 12-month look back period. As the clinical diagnoses were chronic diseases, once identified they were assumed to persist for the duration of follow-up.[21] In addition, we considered the following 3 binary markers of health care utilization as measured over the past 12 months: (1) the presence of 5 or more outpatient visits; (2) 1 or more in patient visits; and (3) dispensing of 2 or more prescription medications other than lipid lowering therapy.[22]

Statistical Analyses

We plotted crude rates of incident lipid lowering therapy as well as rates stratified by age (≥15 vs <15 years) over the study period for all eligible patients. To identify the association between clinical characteristics and lipid lowering therapy initiation, we constructed a nested case-control analysis including all cases of incident lipid lowering therapy use and used incidence density sampling to select one million unmatched controls. We used a nested case-control design instead of a cohort design because of limitations in the computing power required to fit models with time varying covariates and the over 300 million person-months present in the database. Incidence density sampling, which samples controls proportional to person-time, provides direct estimates of the incidence rate ratio and maintains the distribution of covariate person time that would be found in a cohort analysis.[23]

We fit univariable logistic regression models, regressing the outcome of lipid lowering therapy initiation (yes/no) on demographics, clinical diagnoses, and measures of health utilization. We then ran a multivariable logistic regression, modeling the relationship of year and age on initiation of lipid lowering therapy after adjusting for sex and measures of healthcare utilization. In a subanalysis, we included an interaction between age and year to test for the different trends in lipid lowering therapy initiation over time by age group. The effects of time did not differ by age group, and, thus, the interaction term was not included in the final analysis.

We included a secondary analysis limiting our sample to only children with a diagnosis of FH or a dyslipidemia. We compared lipid lowering therapy initiation in this subpopulation by demographics, comorbidities and health utilization. Logistic regression models were constructed along the same