Pediatric polypharmacy

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The frontier of disease therapy is largely composed of new agents targeted against different pathophysiological mechanisms. Many of these therapies are years from entering clinical practice, but what about maximizing the benefits of currently available therapies by applying them earlier in the natural history? The ruptured coronary atherosclerotic plaque is not the beginning of the story, but rather its climax. The disease process starts years earlier with endothelial dysfunction and is grossly visible in the form of fatty streaks, even in young individuals. In this light, treating atherosclerosis in adults is too little, too late.

This has been recognized by a variety of professional associations. For example, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) now includes a category for patients with blood pressures between 120/80 mmHg to 139/89 mmHg known as prehypertension. The American College of Cardiology/American Heart Association classifies stage A heart failure as those at risk for developing heart failure. Predisease has become the disease. The American Academy of Pediatrics has recently taken matters a step further and recommends pharmacological treatment for hyperlipidemia in children as young as eight years of age. Critics of these guidelines and recommendations charge that there is little direct supporting evidence and labeling risk factors as the actual disease is akin to fear mongering and does nothing but add to the population of the 'worried-well' and increase health care costs.

There is little dissent against lifestyle interventions in children for the prevention of adult disease. The controversy lies in the application of pharmacotherapy in asymptomatic children and young adults. There are many barriers to this. The first readily apparent scientific barriers are uncertainty regarding the long-term safety profile of these agents and the absence of clinical trials in these populations. Others are psychological and include the societal notion that taking a medication is a weakness. How will employers and insurance brokers regard applications from medicated youth? There is also the fear that a pharmacological solution circumvents the need and responsibility for the application of more difficult lifestyle interventions. Is a statin a license to continue poor habits? For many, youthful arrogance stipulates a clause on immortality in the bill of rights. The last thing on the mind of the average university student is death and disease perceived to be that of the elderly. This has an important bearing on screening. Many young individuals will only

seek medical attention for symptoms, so even if a statin is proven to be safe and effective if taken for 50 years, it will be a difficult message to communicate.

A recently published editorial (1) on early and aggressive treatment of hypercholesterolemia makes a compelling, eloquent, albeit somewhat circumstantial case in favour of the practice. The need is framed in terms of unprevented expected events. In the landmark Scandinavian Simvastatin Survival Study, the statin arm failed to prevent 70.3% of expected events. The review chides contemporary thinking, which regards the fatty streak as a benign entity not requiring treatment, which transforms into the malignant ruptured plaque. This is akin to withholding cancer therapy until the tumour reaches a certain size. The disease is a continuum and so treatment should be focused on precursors. The case is bolstered by biologically plausible mechanisms through contemporary understanding of the low-density lipoprotein receptor, the functions of the PCSK9 gene (mutations of which have been found to reduce coronary disease by 88%) (2) and animal data. Human data come in the form of epidemiological studies of Japanese patients that have adopted the stereotypical western diet. However, the strongest clinical trial data on the use of pharmacotherapy in youth comes from a two-year study (3) of 214 children between eight and 18 years of age undergoing pharmacotherapy. In this population, there was a significant reduction in the progression of carotid intima-media thickness in those receiving pravastatin with no effects on growth, sexual maturation, hormone levels, or liver or muscle tissue.

The most glaring omission is, of course, the absence of direct long-term data with clinically relevant end points using aggressive dosing regimes. Despite compelling arguments for their efficacy and of biologically plausible ones maintaining safety, there is a large gap of knowledge that spans the step between hypothesis and practice. Witness the recently published Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (4), in which there was a 3.6% absolute or 48% RR increase in cancer within the treatment arm! The results are by no means conclusive but warrant considerable concern before adopting a widespread pharmacological approach.

Lipids are only one long-term risk factor. Compelling evidence links multiple other risk factors in young adults with the development of early atherosclerosis. The most comprehensive data comes from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study (5). The investigators collected arteries, blood and tissue samples

Selected sites

1. JAMA – The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. < http://jama.ama-assn.org/cgi/content/full/289.19.2560v1 >	< http://circ.ahajournals.org/cgi/content/full/112/12/1825 >
2. Circulation – ACC/AHA Practice Guidelines	3. American Academy of Pediatrics
< http://aappolicy.aappublications.org/cgi/content/full/pediatrics;122/1/198 >

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from individuals 15 to 34 years of age who died of an external cause (accidents, homicides and suicides). A risk score that incorporated age, sex, lipids, smoking status, blood pressure, body mass index and glycohemoglobin was constructed and correlated with the presence of atherosclerosis on autopsy specimens. Not surprisingly, a higher risk score was associated with more extensive atherosclerosis. The study stopped short, however, in recommending early pharmacological treatment. Besides advocating policy changes for healthier population lifestyles, the authors suggested that the PDAY risk score could be used in conjunction with noninvasive imaging to treat the highest risk youth.

Some critics have charged that the very debate of instituting pharmacotherapy in children illuminates a societal hypocrisy in our reluctance to institute preventative public health measures yet be willing to medicate disease (6). Perhaps the focus of contemporary primary prevention needs to shift from five- to 10-year risk, to lifetime risk. At the very least, we need to recognize that preventing atherosclerosis will require examination of biological processes in an intergenerational context.

REFERENCES

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3. Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: A randomized controlled trial. *JAMA* 2004;292:331-7.
4. SEAS investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;359:1343-56.
5. McGill HC, McMahan A, Gidding SS. Preventing heart disease in the 21st century – implications of the pathobiological determinants of atherosclerosis in youth (PDAY) study. *Circulation* 2008;117:1216-27.
6. de Ferranti S, Ludwig DS. Storm over statins – the controversy surrounding pharmacologic treatment of children. *N Engl J Med* 2008;359:1309-12.