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Commentary

Statin Therapy in Young Adults

Ready for Prime Time?

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Young adults below 35 years of age who do not have an exceedingly rare genetic disorder such as familial hypercholesterolemia are at very low short-term (5- to 10-year) risk for coronary heart disease (CHD), and lipid-lowering treatment at this stage in life is unlikely to provide any short-term benefit. Current guidelines for the treatment of high cholesterol in young adults are correspondingly conservative and recommend drug therapy (statins) only if cholesterol levels remain very high after a trial of lifestyle modification (1).

In this issue of the *Journal*, reports by Steinberg (2) and Forrester (3) press for earlier and more aggressive treatment with statins, particularly for young adults with high lifetime risk, with the following rationale: 1) atherosclerotic damage to coronary arteries from nonoptimal lipid levels starts accumulating early in life; 2) this damage could be prevented or slowed with statin therapy; and 3) preventing the accumulation of atherosclerotic damage should lead to much lower rates of cardiovascular disease later in life. Multiple lines of evidence, summarized by Steinberg (2) and Forrester (3), support the "cumulative damage hypothesis" and the contention that statin therapy might prevent the damage and thus prevent future cardiovascular events.

Expanding statin therapy indications to include young persons with low short-term risk, however, is a high-stakes proposition that would probably lead to many millions of healthy young adults starting lifelong statin therapy. In this commentary, we discuss uncertainties as to the potential benefits, harms, and costs of initiating statin therapy early in life (Table 1) and the difficult decisions the Adult Treatment Panel of the National Cholesterol Education Program must address in its fourth report, due in early 2011, about whether, and how, to expand statin-prescribing strategies.

Uncertain Benefits

Statin treatment initiated in middle-aged and older populations can arrest and even reverse atherosclerosis (4–6), but its effect on the risk for CHD events is only partial, typically a 20% to 40% reduction compared with placebo in randomized blinded trials (7). In contrast, lowering of low-density lipoprotein (LDL) cholesterol levels to a similar degree but over a lifetime, via genetic variation in the pro-protein convertase subtilisin/kexin type 9 gene that controls expression of the LDL particle receptor, appears to produce near total protection against CHD (88% relative risk reduction) (8). This suggests that reducing lifelong cumulative exposure to LDL via statin therapy initiated early in life may provide more complete protection against future CHD than can be achieved with later life initiation (2,3). Our report from the CARDIA cohort, which reveals a very low prevalence of coronary calcium in middle-aged people who have maintained low levels of LDL cholesterol since they were in their twenties (9), supports this notion.

Important uncertainties remain, however, about how much benefit would be garnered from the untested strategy of initiating statins early in life. First, statin-mediated LDL reduction may not be equivalent to genetically mediated LDL reduction in terms of downstream effects on atherosclerosis and CHD. There is much reason to hope—statins clearly can reduce atherosclerotic disease early in life in some settings (10,11), and atherosclerosis is a strong indicator of future CHD (12,13)—but there is no hard evidence from long-term randomized trials. Second, reducing exposure to LDL in young adulthood starting at age 30 years (as suggested by Steinberg [2]) may not be early enough to prevent the development of significant atherosclerosis and subsequent CHD. Primordial atherosclerotic changes are evident early in life (14), and the initiation of statin therapy after 3 decades of exposure to nonoptimal levels of LDL might provide only modest incremental improvement in terms of atherosclerosis reduction and long-term CHD event protection. Another consideration is that statin trials in middle-aged and older populations reveal that CHD event prevention starts quickly, within 1 to 2 years of initiating statin therapy (7), suggesting that a component of statin efficacy is attributable to plaque stabilization, anti-inflammatory effects, and other short-term "pleiotropic" mechanisms not directly related to arresting the long-term progression of atherosclerosis. To the extent that short-term nonatherosclerotic mechanisms mediate statin efficacy,

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Table 1 Remaining Areas of Uncertainty as to Benefits, Harms, and Costs of Statin Use in Young Adults

Benefits
• Will statins reduce atherosclerotic burden in young adults without familial hypercholesterolemia?
• Will statin-mediated reductions in atherosclerotic burden in young adults lead to reduced CHD event rates later in life?
• How early in life must statin therapy be started, and how intensive should it be to prevent the development of atherosclerosis?
• Will starting statin therapy during young adulthood provide greater protection against CHD events than intensive statin therapy initiated later in life?
• How well will young healthy adults and their physicians adhere to guidelines, and how can adherence be enhanced?
Harms
• Do statins cause myopathy or rhabdomyolysis, diabetes, and other adverse effects at the same rate in young adults as they do in older adults?
• Do the annual rates of these adverse effects increase, decrease, or remain constant with longer-term statin use?
• Are young adults susceptible to any other adverse effects from statins that are not apparent in older adults, and do women at risk of pregnancy require special consideration?
• Does long-term statin therapy (30 to 60 years) cause cancer or other adverse effects at a rate that is high enough to counterbalance expected benefits?
• What are the quality-of-life consequences in young adults of being prescribed lifelong daily medication, and to what extent can these be improved by counseling and other approaches?
Costs
• Can young adults reliably access low-cost generic statins and continue to do so in the future?
• Is there a sufficient enhancement of the reduction in rates of CHD after decades of statin treatment to meet standard thresholds for cost-effectiveness?

CHD = coronary heart disease.

treatment early in life will not provide the expected degree of benefit compared with deferring treatment until later in life, when CHD events usually begin to occur.

In addition to these uncertainties, 2 likely barriers to achieving hoped-for benefits of recommending statins for younger populations will be lack of adherence to guidelines by physicians and by patients. These are substantial problems in older adults at high risk (15–18), and the situation is worse at younger ages (16,17) (the same problem arises with efforts to control hypertension in young adults [19,20]). Mounting efforts to improve adherence to guidelines for physicians and patients at moderate to high short-term risk are probably a more efficient, immediate, and noncontroversial public health strategy than expanding prescribing guidelines into younger age groups (21), although the 2 approaches are not mutually exclusive.

Uncertain Harms

Statins are relatively safe medications and only occasionally have side effects. The most serious, although exceedingly rare, is rhabdomyolysis, estimated from large observational post-marketing studies of middle-aged and older adults to occur at a rate of 3 to 4 per 100,000 person-years of treatment, with 10% of cases being fatal (22,23). Clinically significant myopathy (pain or weakness with elevated creatine kinase) is reported at an excess rate of about 11 per 100,000 person-years in statin users (23). Minor muscle pain (myalgia) is reported commonly by statin users, but this symptom appears to be just as common in persons randomized to placebo as in those randomized to statins in controlled trials (23–25). Persistently elevated serum levels of alanine aminotransferase are estimated to occur at an excess rate of 70 per 100,000 person-years among statin users, although no firm evidence links statin use to liver damage, and rates of liver failure in statin users are indistinguishable from background rates in the population (23,26). Peripheral neuropathy has been reported at a rate of 12 per 100,000 person-years (23). Early concerns about increased rates of cancer and suicide or depression associated with low levels of cholesterol or statin use have not been substantiated by large meta-analyses, longer-term follow-up (10 years) from several clinical trials, and other recent studies (7,27–32). A surprising new finding is the significant increase in diabetes incidence—an excess rate of about 1 in 255 persons taking statins for 4 years—observed in a meta-analysis of randomized trials (33).

Despite these data supporting the safety of statins for most patients, important uncertainty remains. The dearth of long-term follow-up in statin trials makes it unclear whether cumulative risk for these (or other) adverse effects increases with each additional year of treatment. For example, does excess diabetes risk remain at 1 in 255 persons with statin courses longer than 4 years, or does it continue to accrue? If risk continues to accrue at the same rate (about 1 per 1,000 person-years of treatment), then the excess cumulative risk for diabetes after 50 years of treatment (e.g., from age 30 to 80 years) would approach 5% (a number needed to harm of about 21) and would partially counterbalance the expected benefits of statin therapy. Similarly, if the annual rate of statin-associated rhabdomyolysis does not decrease after the first few years but instead continues unabated or even increases with longer-term exposure, treatment for several decades could cause a much higher cumulative risk for this life-threatening condition than we currently see in practice.

Also unknown is how statins affect young adults. We know of no reason why statins should be more toxic in young adults than older adults, but young adults are physiologically different from older adults. It would not be too surprising if myopathy or minor muscle pains, for example, turned out to be more common in young adults, or if young adults were susceptible to some yet undiscovered adverse effect. Young women who may become pregnant are another special case; statins are not considered safe to take during pregnancy or breastfeeding (24,34,35), and this may complicate efforts to extend statin prescribing to young women of childbearing age.

Taking a statin every day for many decades may also alter self-image by "labeling" a person as being less than healthy, induce excessive concern about the prospect of future heart disease, or otherwise dampen quality of life. This is likely to be especially important for young adults who might other-

wise have no regular contact with the medical world. When substantial levels of "disutility" are present and persistent, they can outweigh the benefits of statin therapy (36), which are remote in time and therefore subject to "discounting" (the concept that a person tends to value current events more highly than those in the distant future [37]). However, disutility may wane over time as users become accustomed to the routine of taking a pill every day, and disutility is a modifiable factor: education about the benefits of taking a pill may substantially reduce or even reverse this effect.

Uncertain Costs

With increased availability of low-cost generic formulations, the cost of statins has become less of a limiting factor. In 1 analysis, treatment of all persons age >35 years with LDL levels >130 mg/dl became cost saving (i.e., savings from prevented CHD events outweighed the costs of the medication) when the cost of statins was $0.10 or less (36). Per pill costs in this range are currently available through large discount chains, although prices at retail pharmacies are often substantially higher, even for generic formulations. If very low prices for statins cannot be universally accessed by the public, if average prices rise significantly, if high-cost brand-name formulations are used, or if the added cost of starting statins earlier in life is not sufficiently offset by enhanced reductions in CHD event rates, a major initiative to increase statin prescribing for low-risk young adults could be expensive and not meet standard thresholds for cost-effectiveness.

The Bottom Line

How will the Adult Treatment Panel IV Committee weigh these uncertainties against mounting evidence that supports expanding statin prescribing to young adults? Waiting for more research before expanding statin prescribing guidelines is a reasonable option. Although the ideal randomized trial is essentially impossible because of the decades-long follow-up time required, further observational research on long-term effects (both harms and benefits), confirmation of genetically mediated lifelong cholesterol exposure findings, randomized trials to explore short-term effects in young adults and to improve adherence to guidelines by physicians and patients, and modeling studies to quantify uncertainty and simulate projected effects of different statin prescribing strategies would be feasible and useful for informing guideline changes. This important research should proceed regardless of how guidelines are formulated next year.

If the committee decides to expand treatment guidelines, the approach advocated by Steinberg (2) and Forrester (3) is a reasonable next step: to consider statins for younger persons, perhaps starting at age 30, in those with risk factors that convey high lifetime (as opposed to 10-year) risk for CHD. Treating high-risk persons with more to gain in the long run increases the likelihood that treatment will eventually result in net benefit for patients. This approach will have a limited population-level impact because many events actually occur in the more numerous lower-risk people and thus would fall short of the impact envisioned by Forrester ("unseating coronary disease as the nation's leading killer"). A dramatic expansion of treatment guidelines (including treatment of young adults with lower lifetime risk), along with excellent adherence, would be required to achieve this goal. Such a dramatic expansion in statin prescribing would expose many more people to the uncertain benefits, harms, and costs of lifelong statin therapy and is best approached incrementally by future guidelines.

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