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Reducing Low-Density Lipoprotein Cholesterol After Myocardial Infarction in Older Individuals, Levels Versus Change: Can Observational Studies Answer the Questions?

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Epidemiology studies before the introduction of statin therapy had shown that total or low-density lipoprotein cholesterol (LDL-C) levels at the time of heart attack were directly related to subsequent risk of recurrent myocardial infarction (MI) and death.[1] There was a strong linear relationship between the extent of the reduction of LDL-C and decreased risk of recurrent events after initial heart attack (ie, secondary trials of statin therapy).[2] The change in LDL-C level and lower level of LDL-C were major determinants of the reduction in risk of coronary heart disease (CHD). It has been estimated that for both primary and secondary prevention that a 1-mmol, ≈38-mg, reduction in LDL-C resulted in ≈22% decrease in CHD incidence.[2]

The type of statin therapy, intense or moderate, is directly related to the amount of LDL-C lowering but not necessarily the level reached after starting statin therapy.

A recent meta-analysis suggested that the benefits of more intense versus less intense statin therapy may be restricted to individuals with initial LDL-C >100 mg/dL (ie, before starting statin therapy).[3] The initial results of clinical trials of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors in combination with statin therapy versus statin therapy alone have demonstrated both a greater reduction in LDL-C and decrease in MI but no significant decline in either cardiovascular disease (CVD) or total deaths.[4] This may be, in part, because of the short-term follow up or possibly that the drugs have less effect on cardiovascular mortality. There is less clinical trial evidence on the efficacy of statin therapies for those aged >75 years for both primary and secondary prevention of CHD, resulting in different guidelines proposed for statin therapy in elderly individuals.[5–7] Major concerns for use of statin therapy in elderly individuals include the following: (1) the high prevalence of comorbidities that contribute to disability and death[5]; (2) potential adverse effects of statin therapy on other health behaviors, especially muscle pain leading to a decrease in physical activity and fitness among elderly individuals[8]; (3) polypharmacy and risk of adverse drug interactions; (4) hyperglycemia and diabetes mellitus leading to increased use of antidiabetic drug therapies[9] (this increase in diabetes mellitus may be especially important in the increasing population of older individuals who have obesity, insulin resistance, and hyperglycemia); and (5) the unproved suggestions that lowering LDL-C in elderly individuals might be associated with cognitive decline or depression.

The likelihood of either a placebo or statin clinical trial to evaluate the efficacy of intense statin therapy versus moderate or no statin therapy in the very elderly or the use of PCSK9 inhibitors with or without statin therapy in this very old age group (aged ≥80 years) with long-term follow-up efficacy for multiple end points would be an important contribution, extremely unlikely to occur at least in the United States.

The current article by Alter et al[10] in this issue of the *Journal of the American Heart Association* (*JAHA*) was an observational study and not a clinical trial that evaluated the potential efficacy of intensive versus moderate statin therapy in elderly individuals. The study followed up the participants for up to 8.8 years, but median follow-up was only 2.5 years, a major limitation in interpreting the results of the study.[11] They focused on secondary prevention (ie, individuals had an MI, evaluation of risk of recurrent MIs, other CHD, CVD, and total mortality) ≥30 days after initial MI in relation to the level of LDL-C measured after the heart attack for individuals receiving statin therapy. Individuals not receiving statin therapy were excluded from the study. Their result suggested little further reduction in the number of subsequent heart attacks, other CVD, stroke, CVD, or total mortality if a greater percentage of older individuals, either 65 to 74 or ≥75 years, had LDL-C levels

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reduced to either 70 or 50 mg% by statin therapy after MI. The study does not compare the use of statins with no statin therapy in elderly individuals nor does it measure the change in LDL-C level before and after statin therapy.

Observational studies have certain limitations for interpreting the efficacy of drug therapies compared with a clinical trial. This is especially important in policy decisions that affect large numbers of individuals. What are the problems with this study? First, 61% of the participants in the study had LDL-C <70 mg/dL and 25% had LDL-C <50 mg/dL at the first measurement after their heart attack and had already reached the proposed low levels of LDL-C. These individuals cannot effect change in LDL-C after heart attack and reduction of events. Second, there are no LDL-C measurements before the heart attack so that measure of change in LDL-C before and after starting statin therapy, an important variable in determining reduction in morbidity and mortality (ie, secondary prevention) is missing from the analysis. For example, individuals in this study who had low LDL-C levels may include participants who had low LDL-C levels most of their life because of either specific genetic polymorphisms of LDL-C metabolism or lifestyle characteristics, such as diet (probably unlikely).[12] A small sample of individuals with low LDL-C levels over their lifetime could develop progressive atherosclerosis and subsequent heart attacks at an older age. They may be at risk for a recurrent event, despite their low LDL-C level.

Second, inflammation is also associated with lower levels of LDL-C. Individuals with inflammatory diseases, such as rheumatoid arthritis, have an increased risk of CVD, despite lower LDL-C. There is also increased inflammation with aging.[13]

Third, another group with low LDL-C levels may be individuals who had higher LDL-C levels much of their lifetime but have had a substantial decline in LDL-C with aging, a well-known phenomenon that is associated with increasing morbidity and mortality.[14] Similar declines occur in blood pressure and body weight with increasing aging and are associated with increasing morbidity and mortality.[15]

Fourth, the lower LDL-C levels for those receiving drug therapy may be because of use of more intense versus moderate drug therapy or the greater responsiveness of the individual to the drug therapy. The latter may be partly a genetic determinant and, in part, related to other lifestyles or drug therapies and, most important, to adherence to the drug therapies, a function, in part, of prevalence of adverse effects of drug therapy. The authors report an average number of statin prescriptions over time but not measures of adherence to drug therapies or whether the individuals actually took the medications.

At the other end of the scale, the higher LDL-C levels in these individuals receiving statin therapy can be a function of their higher levels before their heart attack and a similar decrease in LDL-C over time compared with those with lower levels of LDL-C. Poor adherence to the drug therapy or a relative lack of responsiveness to the statin therapy, either intense or moderate drug therapies, likely accounts for a percentage of individuals with higher LDL-C levels while taking statin therapy. A subpopulation of older individuals with high LDL-C may be relatively resistant to the effects of their high LDL-C on the development and progression of atherosclerosis and have their initial heart attacks at older age, possibly primarily related to increased risk of thrombosis or changes in plaque morphological characteristics with aging. They will have first heart attack with lesser extent of atherosclerosis than other individuals. These individuals may also be at lower risk of recurrent heart attacks. Lipid lowering may be of lesser benefit than for the majority of individuals with similar LDL-C levels. This subpopulation can only be identified by measuring extent of atherosclerosis.

There is an increasing prevalence of obesity, insulin resistance, and diabetes mellitus in these older populations (higher remnant particle burden).[16] The measurement of LDL-C level may not provide a true estimate of the level of apolipoprotein B or LDL particles or the type of particles (ie, large or small) that may have a greater impact on atherosclerosis and the risk of heart attack. Other drugs may need to be combined with statin therapy to improve reduction in risk of CHD.[17]

Finally, there is little information about other drug and nonpharmacological therapies, such as use of antithrombotic agents and adherence to blood pressure lowering, that will affect risk of recurrent MI and heart failure.

The study, as noted, has only an average of 2.5 years of follow-up after MI. Statin therapy in elderly individuals may have important longer-term benefits, especially in relationship to the risk of heart failure and especially in combination with antihypertensive drug therapy.[11] Thus, over time, the prevention of heart failure may be reduced with statin therapy but not within the first few years. Similarly, statin therapy has recently been shown to be highly beneficial in reducing the complications of peripheral arterial disease.[18]

In conclusion, clinical trials consistently demonstrate that the change in LDL-C levels is associated with a substantial reduction in the risk of CHD. Second, older chronological age is not the same as older biological age. The decision about the intensity of the statin therapy (ie, moderate versus intense or even potential use of PCSK9 inhibitors) should probably be based on measures of biological aging and comorbidity (ie, degree of disability, frailty, cognitive dysfunction, and sarcopenia) rather than just a specific chronological age. Third, a low cholesterol level in an older individual may be attributable to poor health rather than good health and may be associated with increased mortality, a paradox similar to that observed with lower blood pressure levels in elderly individuals. Such information should not be used to presume that low

cholesterol levels over a lifetime among elderly individuals are associated with increased mortality and, therefore, that statin therapy should not be used in elderly individuals. Fourth, a primary determinant of CVD in both middle-aged and older individuals is the extent of atherosclerosis, which can be easily measured by computed tomography with low radiation effects and at relatively low cost.[19] If there is question about whether to start or not start statin therapy or intensive or moderate-intense statin therapy in elderly individuals, measurement of coronary atherosclerosis may be an approach to evaluate the likelihood of recurrent cardiac events and benefits of statin therapy. Finally, lack of adherence to statin therapy is a major player in the continued high morbidity and mortality of CVD after a heart attack. A focus on enhancing adherence to statin drug therapy is probably more important in the community than a continued debate on whether the LDL-C level should be reduced to 70 or 50 mg%.[20]

Disclosures

None.

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