somewhat different

This paper explores the background changes to the low cholesterol guideline in hr | Ascent

Treatment Related Very Low Levels of LDL-Cholesterol – Is There a Mortality Risk?

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An elevated level of low-density lipoprotein (LDL) cholesterol is a major risk factor for the development of coronary artery disease (CAD). Lowering elevated values is one of the cornerstones of the treatment for the condition. Traditionally, the goal was to lower the LDL-cholesterol value to less than 70 mg/dl but currently a greater than 30% reduction from pre-treatment readings is the rule. Statin drugs have been the primary agents for achieving these goals. Most studies have indicated that the lower the LDL-cholesterol, the lower the cardiovascular risk.

With the availability of a new class of lipid lowering drugs, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, ones that prevent the degradation of LDL receptors, the achievement of markedly reduced levels of LDL-cholesterol (30 mg/dl or lower) is now possible.

However, questions have been raised about whether lowering the LDL-cholesterol to such low values can lead to an increase in all-cause mortality. Studies on the risk related to total and LDL- cholesterol levels have shown a U shaped

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curve, with an increased death rate at very low and very high values. This risk pattern persisted despite controlling for multiple comorbid conditions and with the exclusion of deaths within the first three or more years after initial entry into the study. In addition, there was an increased risk of death due to cancer, hemorrhagic stroke, heart failure and infections with lower values. This early data did not clearly delineate if this risk was present in both treated and untreated individuals.

Several recent papers seem to have settled this issue. A large prospective study from Denmark by Johannesen et al. looked at the all-cause mortality associated with LDL-cholesterol in over 108,000 individuals. Adjustment was made for a wide variety of factors including; age, sex, smoking history, systolic blood pressure, diabetes, cancer, cardiovascular disease, COPD and treatment for hyperlipidemia. As with prior studies, there was a clear U shaped curve with a higher relative risk for death at the lowest and highest values (actually highest at the lower end).

However, dividing the overall group into those with and without lipid lowering therapy, revealed a clear difference. The U shaped curve remained at the extremes in the untreated group i.e. a very low LDL-cholesterol was a marker for an increased death rate. For the treated group, the curve changed to a J shape, one that showed increased mortality only at the high values. Low LDL-cholesterol readings resulting from treatment did not significantly increase death rates. This, pattern persisted in those over age 65 and with the exclusion of individuals with less than five years of follow-up and known cardiovascular disease, cancer and COPD at baseline.

In addition, multiple other studies have indicated that lowering the LDL-cholesterol values to 50 mg/dl or lower using statins, PCSK9 inhibitors or a combination of the two, has not lead to an increase in all-cause mortality. Furthermore, there has been no indication that the risk of neurocognitive decline, hemorrhagic stroke, cancer, infections or impaired steroid hormone synthesis has resulted from the achievement of these very low LDL-cholesterol readings.

Thus, while the occurrence of low total and LDL-cholesterol (representing 60-70% of the total) values is a clear marker for increased mortality in untreated individuals, there is no evidence that comparable levels are a problem in those who achieve them through lipid lowering therapy.

In light of this data, the Low Cholesterol guideline in the hr | Ascent underwriting manual was changed.

In keeping with the information noted above, treated applicants with a low LDL-cholesterol, who otherwise meet minimum acceptable criteria are not rated or excluded from consideration for the best available preferred class.

One change from the past is that the new guideline for treated individuals uses total cholesterol readings only if the LDL-cholesterol value is not available.

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Low Cholesterol References:

1. Johannesen CDL, Langsted A, et al., “Association between Low Density Lipoprotein and All Cause and Cause Specific Mortality in Denmark: A Prospective Cohort Study”, BMJ, 2020; 371:m4266.
2. Sung KC, Huh JH, et al., “Low Levels of Low-Density Lipoprotein Cholesterol and Mortality Outcomes in Non-Statin Users”, J Clin Med, 2019; 8, 1571; doi:10.3390/jcm8101571.
3. Faselis C, Imprialos K, et al., “Is Very Low LDL-C Harmful?”, Curr Pharm Des, 2018; 24:3658-3664.
4. Bandyopadhyay D, Qureshi A, et al., “Safety and Efficacy of Extremely Low LDL-Cholesterol Levels and Its Prospects in Hyperlipidemia Management”, J Lipids, 2018 Apr 23;2018:8598054. doi: 10.1155/2018/8598054. eCollection 2018.
5. Giugliano RP, Wiviott SD, et al., “Long-Term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol: A Prespecified Analysis of the IMPROVE-IT Trial”, JAMA Cardiol, 2017; 2:547-555.
6. Ray KK, Ginsberg HN, et al., “Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 Odyssey Trials Comparing Alirocumab with Control”, Circulation, 2016; 134:1931-1943.
7. Hsia J, MacFayden JG, et al., “Cardiovascular Event Reduction and Adverse Events Among Subjects Attaining Low-Density Lipoprotein Cholesterol < 50 mg/dl with Rosuvastatin: The JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin)” J Am Coll Cardiol, 2011; 57:1666-1675.