

## High density lipoprotein cholesterol and risk of death

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Seminal findings from the Framingham Heart Study established that low levels of high density lipoprotein cholesterol (HDL-C) are associated with increased risk of cardiovascular outcomes and death. The findings lent plausibility to the hypothesis that higher levels of HDL-C would be associated with improved cardiovascular outcomes and reduced mortality. This hypothesis was never thoroughly tested in that none of the prior studies—which involved few thousand patients, where very few cohort participants had very high HDL-C levels—were powered enough to rigorously address this clinically relevant question. It was also assumed that raising HDL-C levels will lead to improved cardiovascular outcomes and reduced mortality. The assumed veracity of the hypothesis powered the undertaking of multiple randomized controlled trials including those testing niacin, and those involving cholesterol ester transfer protein (CETP) inhibitors. These pharmaceutical intervention studies successfully resulted in increased HDL-C levels, but did not result in amelioration of cardiovascular outcomes or mortality (2-4).

Recent experimental evidence suggests that HDL-C exhibits a biphasic effect (at low and high concentrations); where at high concentrations, HDL-C paradoxically promoted senescence and abrogated endothelial progenitor cell tube formation and angiogenesis. The findings indicate that the protective effect of HDL-C is vitiated at higher

concentrations (5). Recent Mendelian randomization analyses show that genetic mechanisms that raise plasma HDL-C do not result in lowering the risk of myocardial infarction (6).

In a large epidemiologic study involving 1.7 million United States Veterans followed for over 9 years (16 million person-years) we evaluated the relationship between HDL-C and risk of death; we found that low HDL-C is associated with increased risk of death, and—unexpectedly—that high HDL-C is also associated with increased risk of death. The relationship between HDL-C and risk of mortality exhibited a U-shaped association where risk of death is increased at low and high HDL-C levels (1). The findings were also consistent in studies where we examined the relationship of HDL-C and risk of incident kidney disease and its progression to end stage renal disease (likely a result of microvascular injury and disease), where again the salutary effect of high HDL-C was reversed at high concentrations and risk relationship was U-shaped (7). Ko and colleagues recently reported results consistent with ours, and also showed increased cardiovascular and non-cardiovascular mortality at both low and high HDL-C levels; they noted that HDL-C is does not represent a cardiovascular specific risk factor given that it is also associated with non-cardiovascular outcomes (8).

Taken together, the constellation of findings suggests that HDL-C is a non-specific and heavily confounded measure, and represents a poor marker for cardiovascular

outcomes. It should not be regarded as an independent modifiable risk factor for cardiovascular disease, and is an unreliable target for pharmaceutical interventions. Moving beyond quantitative HDL-C levels to a qualitative assessment of HDL-C size, composition, functional capacity or HDL-C subclasses may be promising (9,10).

### The promise of big data in medicine

Another important lesson we learned is that foundational studies such as the Framingham Heart Studies and others significantly advanced our understanding of cardiovascular health and disease, and specifically elucidated the relationship between cholesterol parameters (and of particular relevance here: HDL-Cholesterol) and clinical outcomes. However, these studies are limited in that the number of patients in these longitudinal cohorts is relatively small compared to what could be obtained using a Big Data approach. The recent epidemiologic reports which unearthed the finding that high HDL-C is associated with increased risk of death leveraged the power of Big Data to examine the relationship across the full range of HDL-C values spectrum. This approach of using the powerful lens of Big Data to re-examine perennial questions, and challenge prior knowledge and prevailing assumptions holds significant promise and –in our opinion- will yield a more a more nuanced understanding of health and disease in the decades to come.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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