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Ezetimibe, Risk Stratification, and Secondary Prevention

The recent report of Bohula et al. (1) regarding ezetimibe use in the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) trial and atherothrombotic risk lends support to 2 fundamental theories of cardiovascular disease prevention: 1) lowering cholesterol reduces the risk of cardiovascular events (the cholesterol hypothesis); and 2) risk models can be used to guide lipid-lowering therapy (1). Before extending these findings to clinical practice and accepting this study as providing landmark proof of concept, we should carefully consider several caveats and counterpoints (2). The IMPROVE-IT trial reported no mortality benefit and the primary endpoint barely achieved statistical significance (hazard ratio: 0.936; 95% confidence interval: 0.890 to 0.990) despite enrolling >18,000 patients followed for nearly 7 years (3). Furthermore, 42% of the IMPROVE-IT trial participants prematurely stopped taking their study medications (3). These findings must also be reconciled with the only other published randomized trial of ezetimibe added to background statin therapy (ENHANCE [Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression]), which reported more deaths and cardiovascular events in the ezetimibe group (4). Although the ENHANCE study was not designed to primarily assess clinical events, these untoward outcomes should not be ignored. The risk model proposed by Bohula et al. (1) did accurately demonstrate that the highest-risk patients experienced the greatest clinical benefit. However, 350 patient-years of treatment with ezetimibe were required to avoid 1 primary endpoint event in the IMPROVE-IT trial (2). Notably, the Bohula et al. (1) study also utilized a different primary endpoint than the original IMPROVE-IT trial did. Utilizing cardiovascular risk to guide lipid therapy is commonly recommended, but there is substantial evidence that this model does not consistently identify patients who may or may not benefit from lipid-lowering therapy (5). Moreover, there are nearly 4 dozen well-conducted randomized controlled trials of cholesterol lowering that have failed to demonstrate a reduction in mortality or cardiovascular events (4). The Bohula et al. (1) study was well designed, conducted, and thought provoking, but I believe the conclusions should be considered hypothesis generating rather than hypothesis proving.

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