more formal development of a possible target trough concentration range.

An example of a range for this individual may be derived by adjusting the lines of best fit of the event risk–concentration curves by using event weighting according to the hazard ratios of death described by Eikelboom et al. (8) and then combining the lines of best fit (Fig. 1). Note that for the patient described here, the therapeutic range is relatively narrow compared with the 10th to 90th percentiles of trough concentrations and would certainly not be considered a wide therapeutic range.

4. Trough concentrations outside the 10th and 90th percentiles.

By definition, 20% of individuals treated with dabigatran etexilate in the RE-LY study had concentrations outside the 10th to 90th percentiles of trough plasma dabigatran concentrations. Did the outcomes for these individuals differ from the rest of the cohort? Dose adjustment to "improve" the drug exposure for these 20% of patients may be beneficial. Could the authors describe the characteristics of the individuals with trough plasma dabigatran concentrations that were below the 10th percentile and above the 90th percentile?

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The Missing Link Between High-Density Lipoprotein Cholesterol and Inflammatory Response in Cardiovascular Disease

In the recently published post-hoc analysis from the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, low high-density lipoprotein cholesterol (HDL-C) levels remained a powerful and independent predictor of cardiovascular (CV) risk in 2,193 patients with stable ischemic heart disease (1). This finding was also confirmed in patients with low-density lipoprotein cholesterol (LDL-C) levels <70 mg/dl. However, both in primary prevention, as in the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial (2), as in secondary prevention (3), potent statin therapy may lead to no relation between HDL-C and residual CV risk. Furthermore, the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) Investigators have shown that there was no incremental clinical benefit from the addition of niacin to statin therapy despite a significant and sustained increase in HDL-C (4).

We feel that the missing link to understanding this unclear relation of HDL-C and residual CV risk in patients using intensive lipid-lowering medication relies on the degree of systemic inflammation. In fact, although HDL-C modulates cholesterol availability in the cell membrane, which promotes reverse cholesterol transport (HDL-C's main antiatherogenic effect), it also influences the immune response, the hematopoietic stem cells maturation, and ultimately the leukocyte number (5–7). HDL-C also plays a key role in the humoral innate immune response, as HDL-C induces the long pentraxin 3 (PTX3), and PTX3 levels are increased in animal models with genetically increased HDL levels. PTX3 deficiency then results in increased inflammation and bone marrow monocytosis (8). Again, in a prospective multiethnic trial that enrolled patients with ST-segment elevation myocardial infarction (9), high levels of systemic inflammation, defined by increased levels of interleukin-6 and C-reactive protein (CRP) within 6 h of the onset of symptoms, were associated with a significant reduction in HDL-C compared with patients with ST-segment elevation myocardial infarction and low levels of systemic inflammatory markers (10). Furthermore, inflammation induces major changes in HDL-C composition. Mediators of inflammation such as tumor necrosis factor–alpha and interleukin-6 induce expression of serum amyloid A and group IIA secretory phospholipase A_2, which dramatically alter HDL apolipoprotein content and levels, respectively (7). All this evidence suggests a profound link between inflammatory response in patients with atherosclerosis and the levels and composition of HDL-C. In our opinion, this link is underexplored in the subanalyses of large clinical trials aimed at increasing HDL-C levels and in studies on the predictive value of HDL-C levels on residual CV risk.

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Have the authors investigated in their post-hoc analysis (1) whether HDL-C levels were associated with alterations in whole blood count or other established immune-inflammatory markers, such as CRP? Can the whole blood count or CRP levels limit the power of prediction of HDL-C when adjusted for inflammatory markers?

As a further speculation, the limited clinical benefit of niacin or cholesteryl ester transfer protein inhibitors, despite effective increases in HDL-C levels (4,11), could be associated with an inconsistent enhancing effect on immune-inflammatory response or with the modulation of HDL subclasses unable to tune immune response during atherogenesis.

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Mechanisms Explaining the Relationship Between Metabolically Healthy Obesity and Cardiovascular Risk

Recently, much interest has been given to the novel concept of metabolically healthy obesity (MHO). It could help to direct the limited resources that are available for prevention of metabolic diseases to the people at highest risk (1). Mørkedal et al. (2) now showed that individuals with MHO are not at increased risk of acute myocardial infarction (AMI) compared with normal-weight, metabolically healthy subjects. In contrast, they have an increased incidence of heart failure (HF) (2). Lavie et al. (3) convincingly discussed mechanisms, explaining why obesity itself, and not necessarily only metabolic abnormalities such as hypertension, dyslipidemia, hyperglycemia, and subclinical inflammation, has an impact on the development of HF. Most recently, a meta-analysis questioned the concept of MHO for its relevance for cardiovascular events (4). The study of Mørkedal et al. now can show that it is necessary to separate the predictive effects of MHO on AMI and HF when it comes to the prediction of cardiovascular disease.

The study by Mørkedal et al. (2) cannot provide mechanisms explaining the lower risk of AMI in those with MHO compared with subjects with metabolically unhealthy obesity. We could show that MHO is associated with a moderately reduced visceral fat mass, but, more importantly, with a largely reduced liver fat content (5). We also provided evidence that genetic variability in the adiponectin receptor 1 gene determines the prevalence of MHO and that MHO correlates with lower levels of the liver-secreted glycoprotein fetuin-A (5). Particularly lower production of this proinflammatory hepatokine, which affects glucose and lipid metabolism and induces subclinical inflammation (6,7), may explain the lower risk of AMI in MHO.

Regarding preventive strategies in MHO, Mørkedal et al. (2) refer to a small study indicating that lifestyle intervention may decrease insulin sensitivity and thus be harmful for people with this condition (8). However, we could show in a larger study that visceral fat mass decreased and insulin sensitivity remained high during a lifestyle intervention in subjects with MHO (9).

The concept of MHO has gained much interest in the scientific community. However, because of its complex nature and the not fully understood mechanisms involved in the causes and consequences of MHO, it is very important to carefully deal with this popular concept when it comes to the prediction and prevention of metabolic diseases.

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