Table 1. Ranking of the Most Discriminating Criteria Used in Randomized Controlled Severe Asthma Trials

Criterion	Patients Excluded Because of the Criterion (%)
Reversibility	73
Exacerbation rate	58
Absence of oral corticosteroid treatment	50
No ICU admission history	31
Maximum FEV_1	24
Minimum FEV_1	23
Smoking status	23
Age	10
BMI/weight	3
Comorbidities	2

Definition of abbreviations: BMI = body mass index; ICU = intensive care unit.
Percentages are out of the total number of patients in the COBRA (Cohorte Obstruction Bronchique et Asthme) cohort.

drugs, such as age, bronchodilator reversibility, and history of or current tobacco use. Naturally, some criteria may be warranted by the trial methodology to reach the primary endpoint. For example, the minimum exacerbation rate in the previous year may guarantee a sufficient number of events to avoid studies being prolonged if the primary endpoint is the time until the first exacerbation. These administrative and financial constraints should not, however, affect the scientific value of these studies, and the results should remain able to be extrapolated to excluded populations.

Patients included in RCTs are young, are recently diagnosed, are healthy other than their asthma, have moderate to severe rather than very severe asthma, and have never been heavy smokers. Because current guidelines such as GINA rely on results from such exclusive RCTs, this calls into question the extent to which these guidelines are applicable to daily practice. ■

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A Potential Link between Serum Low-Density Lipoproteins and Asthma

To the Editor:

We read with great interest the article by Barochia and colleagues about the relationship between serum lipid and apolipoprotein levels and asthma (1). As highlighted by the authors, although apolipoproteins and lipoproteins are important modulators of inflammation, varying relationships exist between these parameters and asthma (2), and the data are still not conclusive. Indeed, it is still not fully clear which lipoproteins are more strictly associated with asthma development and progression (severity).

Barochia and colleagues report a positive correlation between FEV_1% predicted and high-density lipoprotein (HDL)-cholesterol or apolipoprotein A-I in atopic asthma, and they also suggest that this correlation may be largely mediated by the subfraction of large HDL particles. This finding seems to complement what we

reported in 2013 in another study on the association between asthma and low-density lipoprotein (LDL) subclasses (3): We found a positive correlation between FEV_1% predicted and larger LDL particles (LDL-1), as well as negative correlation between FEV_1% predicted and smaller, more dense LDL particles (LDL-3). In that study, we hypothesized that LDL could represent a potent trigger for the inflammatory changes of the airways. It was somewhat surprising that the Barochia and colleagues did not mention our study, as it still represents the only study that has assessed the full spectrum of all seven LDL subclasses in asthma.

As highlighted by the European Panel on LDL Subclasses (4), the methodology used for assessing lipoprotein subclasses is crucial. In the present study, Barochia and colleagues used nuclear magnetic resonance spectroscopy to assess the lipoprotein particles; yet with this methodology, they were able to assess only a few subclasses with low resolution (e.g., three very-low-density lipoprotein subclasses [large, medium, and small very-low-density lipoprotein], two LDL subclasses [large and small LDL], and three HDL subclasses [large, medium, and small HDL]). Methodologies are available to assess lipoprotein subfractions with a higher degree of resolution, and in our study, we used a methodology of gel electrophoresis (Lipoprint; Quantimetrix Corporation, Redondo Beach, CA) that is able to distinguish seven LDL subclasses (3) as well as 10 HDL subclasses (5).

Of interest, in our study (3), we reported that asthma was associated with smaller LDL particles, which are proinflammatory particles (6), and in the present study, Barochia and colleagues reported that asthma was associated with larger HDL particles, which seem to be dysfunctional HDLs with proinflammatory properties (7). We therefore believe that the findings of the two studies support the concept that small LDLs could lead to the amplification of the inflammatory cascade in asthma, and we advocate for larger studies specifically designed to confirm the association between asthma and dyslipidemia and to elucidate the underlying mechanisms. ■

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Reply

From the Authors:

We thank Drs. Scichilone and Rizzo for bringing to our attention their study investigating the association between lung function in patients with asthma and subclasses of low-density lipoproteins (LDLs), as measured by gel electrophoresis (1). In particular, the finding that the LDL-3 subclass is negatively correlated with FEV_1 after adjusting for differences in age, sex, and body mass index is intriguing. We believe their result is consistent with the negative association we found between percentage predicted FEV_1 and subgroups of LDL particles, as measured by nuclear magnetic resonance (NMR) spectroscopy in atopic patients with asthma.

We respectfully point out that we did not report an association between asthma and large high-density lipoprotein (HDL) particles but, rather, a positive association between FEV_1% predicted and the concentration of large HDL_{NMR} particles in patients with asthma (2). Thus, we postulate that large HDL_{NMR} particles may modulate the severity of airflow obstruction in atopic patients with asthma.

The study of the significance of lipoproteins in asthma is in its early stages yet. We agree with Drs. Scichilone and Rizzo that additional studies investigating the composition and function of subclasses of lipoprotein molecules, and the various methods used to measure them, will be necessary to better characterize the precise roles they may be playing in the pathogenesis of asthma. ■

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