CORRESPONDENCE

The Treatment of Disorders of Lipid Metabolism

by Prof. Dr. med. Klaus G. Parhofer in issue 15/2016

Fixed-dose Strategy Is Lacking

Parhofer deserves thanks for his excellent summary of the current state of research into treating lipid metabolism disorders (1). However, as a primary care physician I wish to challenge him on two issues.

- Parhofer writes himself that in the IMPROVE-IT Study, ezetimibe did not lower cardiovascular nor all-cause mortality, in spite of a very large number of participants and a number needed to treat (NNT) of 350/year. Four pages later, however, he recommends exactly this treatment.
- The readership aimed at with this review article consists of primary care physicians too. It is therefore surprising that Parhofer addresses merely the target value strategy, as recommended by the German Society of Cardiology and the German Society of Internal Medicine, but not the equally well-founded strategy of the fixed dose, as discussed by the German College of General Practitioners and Family Physicians (DEGAM) in the national clinical practice guideline on chronic coronary heart disease (3) or the US ACC/AHA guidelines of 2013 (4).

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Dr. med. Thomas Maibaum
Rostock
Thomas.maibaum@yahoo.de

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Distorted Perspective

On the basis of my own experience, I agree with the author: most patients with symptomatic atherosclerosis will have to be treated with statins. This is not because an appropriate diet is ineffective—as is the view often promulgated by the pharmaceutical industry, for obvious reasons—but because patients will insist that they adhere to the diet but rarely actually do so in practice. I am a vegetarian myself, and as a result of my own convictions, an above average proportion of my patients are also vegetarians or even vegans. I cannot spontaneously recall any of them who have clinically manifest atherosclerosis, and I have practiced as a specialist in internal medicine for almost 30 years. The cholesterol measurements of the vegetarians and vegans are below 200 mg/dl in 80% of cases, and there is therefore no indication for measuring LDL.

The problem is that cardiologists, angiologists, diabetologists, and endocrinologists/lipid specialists only ever get to see persons who consume an unhealthy diet and suffer the consequences, but who do not readily admit this. This distorts perceptions among the medical specialists mentioned above.

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Dr. med. Peter Pommer
Abteilung für Pneumologie, Fachklinik Allgäu, Pfronten drpommer@gmx.de

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Genetic Factors

Parhofer in his article explains that the lipoprotein(a) concentration is mostly genetically determined. Furthermore, he recommends that it needs to be measured only once, with a second measurement for confirmation if required (1).

Although the therapeutic options available so far are limited—as explained by the author in his review article—the general recommendation of a once-only measurement should be challenged. Kostner et al. described that lipoprotein(a) concentrations can be affected by a number of non-genetic factors. These include liver disease, terminal renal failure, diabetes mellitus, but also the effects of alcohol, medications, and hormones. As a result, values may be raised as well as lowered (2). Depending on the comorbidity/medication, follow-up measurements of lipoprotein(a) concentrations may make sense. Kostner et al. provide a detailed overview for different patient groups and make recommendations regarding examination intervals (2). Another study also reported individual, large variations in measurements. For this reason, repeat measurements are certainly worth discussing (3). From the perspective of laboratory medicine, consideration should be given to the commercial assay that was used to measure lipoprotein(a) and whether the respective measuring method is independent of apo(a) isoforms. In follow-ups, it is therefore important to assess whether the measurements were obtained by using the same method each time.

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Dr. med. Ramona Dolscheid-Pommerich
Prof. Dr. med. Dipl. Biol. Birgit Stoffel-Wagner
Institut für Klinische Chemie und Klinische Pharmakologie
Universitätsklinikum Bonn
ramona.dolscheid-pommerich@ukb.uni-bonn.de

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Balanced Contribution

Professor Parhofer takes a balanced approach in his article on disorders of lipid metabolism. He mentions that no consensus exists internationally on whether defined target LDL concentrations should be attained or whether medications other than statins should be used. And he writes that the benefit of LDL targets has never been confirmed. How relevant is a finding of plaque regression on intravascular ultrasonography? It is possible that communicating the LDL concentration to the patient may improve adherence to statin treatment. However, we think it is better to decide in partnership with the patient what their treatment should be—by using ARRIBA (www.arriba-hausarzt.de), for example. Is the classification into different lipid disorders really clinically relevant? Are nutritional/dietary recommendations actually still sustainable? What benefit does therapy using high doses of statins really confer in acute coronary syndrome? One of the cited studies showed a benefit for high doses with regard to inpatient admission and revascularization, but none for (re-)infarction rates and all-cause mortality. The other study compared atorvastatin not with low-dosage statins but with placebo—this is not proof of any benefit of high doses. The recommendation of the Drug Commission of the German Medical Association (Arzneimittelkommission der Ärzteschaft) and of US specialist societies—that of not controlling lipids when the indication for statin treatment is given—remains unrefuted.

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Dr. med. Günther Egidi
Bremen, guenther.egidi@posteo.de

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Too Many Competing Interests

The review article on the treatment of dyslipidemias (1) unfortunately mentions the clinical practice guideline NVL-KHK (2), which is definitive in Germany, in one sentence only. Instead, what follows is the therapeutic recommendations of the European Society of Cardiology (ESC) and the pharmaceutical industry: "LDL—the lower, the better." The NVL-KHK guideline (S3 level, 2016) clarifies, however, that an LDL target value is not supported by the available evidence: "The LDL target value <100 mg/dl is therefore based on expert opinion" (2).

In the meantime, the transparency portal Leitlinienwatch.de [guideline watch] has drawn attention to a neglected aspect: the 2011 ESC dyslipidemia guideline that is used by all those in favor of "treating to target" is subject to numerous conflicting interests and therefore does not meet the quality criteria of the Association of the Scientific Medical Societies in Germany (AWMF) (3, 4):

- 17 out of a total of 18 authors have competing interests, 12 of these relating directly to the subject of the guideline.
- 22 of 29 document reviewers reported conflicts of interest, 15 of these relating directly to the subject of the guideline.
- The guideline documentation does not contain any mention of abstentions regarding competing interests.
- No public review has taken place (2).

On this background, the therapeutic algorithm suggested in *Deutsches Ärzteblatt*, using ezetemibe and PCSK9-inhibitors, is questionable, not least because the authors also reported financial ties to the manufacturers of the recommended products.

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Dr. med. Niklas Schurig
Board member of MEZIS e. V., Member of leitlinienwatch.de
Kuppenheim
schurig@mezis.de

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The authors declare that no conflict of interest exists.

In Reply:

Maibaum questions in his letter why, in spite of lacking any effect on all-cause mortality, treatment with ezetimibe is recommended in certain circumstances.

The IMPROVE-IT Study showed that the primary endpoint (cardiovascular events) can be reduced significantly. If secondary endpoints are also changed (or not, as the case may be) that obviously deserves mentioning and is worth discussing, but this does not change the primary conclusion of the study. It is therefore correct that ezetimibe can, and should, be used in certain patients in certain circumstances. This is now also stated explicitly in the revised US recommendations (1).

The second question is whether target-oriented therapy is really superior to a "fire & forget" strategy. In addition to the fact that some patients respond better than others to certain treatments (consequently, higher or lower doses can be usefully deployed) it was shown that a "fire & forget" strategy is associated with poorer compliance and poorer cardiovascular survival (2). Let me re-emphasize that the US ACC/AHA guidelines of 2013 do not propose an exclusively fixed-dose strategy but that the authors assume that high-dose statin treatment results in a reduction in LDL concentrations of >50% and treatment with a moderate dose to a reduction of 30–50% in LDL. This may vary substantially in the individual case, so that measurements and adapting the strategy seems sensible (1, 3).

Egidi in his letter touches on many interesting questions that are of great relevance in clinical practice. Plaque regression on intravascular ultrasound correlates—in as far as data are available on this—with the rate of cardiovascular events; consequently, such studies continue to have an indicator function for outcomes trials, which are to be conducted at a later date.

It is entirely correct that communicating LDL cholesterol concentrations and discussing target values improve patients' adherence to statin treatment. It seems obvious that patients have to be included in this process.

The clinical classification of dyslipidemias helps to decide which strategy is most likely to yield the desired outcome. Hypertriglyceridemia is very sensitive to lifestyle measures, but in patients with increased LDL cholesterol values this is not a promising approach. Nutritional/dietary recommendations regarding hypertriglyceridemia (almost complete alcohol abstinence, reduction in intake of rapidly metabolized carbohydrates) have changed little in recent years. Regarding dietary cholesterol intake, recent data have shown that this is likely to affect cholesterol concentrations to a very limited degree, but these findings have not remained unopposed (4, 5).

Schurig in his letter emphasizes that the ESC guidelines and the suggested therapeutic algorithm are of questionable value because of numerous conflicts of interests. This does not change the fact that statin treatment and combined treatment with a statin and ezetimibe have been investigated in endpoint studies and were found to be superior.

In translating this evidence into concrete instructions for action, a certain scope for interpretation remains, for example as a result of considering and weighting additional evidence. Defining target values is one possible interpretation, and as a result of this, the suggested algorithm. The article explained in detail that unequivocal studies showing superiority for target-oriented therapy with a relevant algorithm are lacking, but in the author's view, numerous arguments speak in favor of delivering target-oriented therapy following the suggested algorithm (6).

Dolscheid-Pommerich and Stoffel-Wagner in their letter raise the problems associated with measuring lipoprotein(a). However, the fact is that in spite of a strong genetic determination and the negligible effect of exogenous factors, lipoprotein(a) levels are subject to a certain amount of variability. However, usually this does not mean dramatic changes in lipoprotein(a) concentrations. For the purposes of risk assessment, however, a rough classification (normal, slightly raised, strongly raised, very strongly raised) is usually sufficient. When evaluating consecutive levels in an individual patient, attention has to be paid to the methods that were employed, as these may have an effect on the measurements.

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Prof. Dr. med. Klaus G. Parhofer
Klinikum der Universität München
Medizinische Klinik II, Großhadern
klaus.parhofer@med.uni-muenchen.de

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