

Brotherhood of genetics and preventive medication

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Online publish-ahead-of-print 7 May 2015

This editorial refers to ‘Genetic variation in the cholesterol transporter NPC1L1, ischaemic vascular disease, and gallstone disease’[†], by B.K. Lauridsen *et al.*, on page 1601.

Even nectar is poison if taken to excess.

Hindu Proverb

Disease from lack of balance

Staying in good health requires balance and harmony. This seems to apply specifically to the Niemann–Pick C1 Like 1 (NPC1L1) protein. If the transporter’s activity loses balance, i.e. absorbing either too little or too much cholesterol in the liver and intestine, the cholesterol concentration goes up either in bile or in serum. In the long run this may translate into either one of two evils: gallstones or a heart attack.

This conclusion is brought about by a study presented by Lauridsen *et al.*¹ in this issue. The authors used a Mendelian randomization approach² for studying the chromosomal locus of *NPC1L1* and its inter-relationship with serum cholesterol and complex phenotypes.¹ The transporter facilitates hepatic and intestinal cholesterol absorption.³ A higher activity removes more cholesterol from bile but increases its concentration in serum. Not surprisingly, the authors observed that presumably more active variants of *NPC1L1* occur with higher serum cholesterol levels.¹ The same variants increased the odds for vascular disease but had opposite effects on hospitalizations for gallstone disease.¹ The apparent explanation for this quandary seems to be obvious. NPC1L1 contributes to the fate of cholesterol. Atherosclerosis is promoted when too much is reabsorbed into the serum. Vice versa, cholelithiasis occurs when bile is left with too much cholesterol and not enough bile salts.

How to find the optimal balance

For clinicians, the data are interesting not only due to the fact that NPC1L1 modulates the risk of disease but also because the

transporter is the target of ezetimibe, a drug used for lowering LDL cholesterol.³ It has been debated for a long time whether ezetimibe also lowers cardiovascular risk.⁴ The data from the present and two previous genetic studies strongly support the notion that ezetimibe’s mode of action, i.e. inhibiting NPC1L1, is an appropriate target.^{1,5,6} Indeed, naturally occurring loss-of-function variants of *NPC1L1* occur together with a markedly decreased risk of atherosclerotic vascular disease⁵ (Figure 1). Along the same lines, a long awaited—and not yet published—clinical trial, IMPROVE-IT, revealed that ezetimibe decreases cardiovascular events in high-risk subjects with coronary syndromes. Thus, the drug does what it is supposed to do.⁷

However, in the study of Lauridsen *et al.* we learn that genetic variants that mimic the action of ezetimibe may also lower cholesterol absorption from bile and thereby increase the risk of gallstones.¹ Indeed, experimental studies on ezetimibe in dogs and mice came to similar conclusions in that the drug may increase biliary cholesterol concentration (for references see Lauridsen *et al.*¹). Fortunately, it appears that this potential side effect of the drug is ameliorated by concomitant use of statins, which may lower the risk of gallstone formation.⁸ Nevertheless, future analyses of data from IMPROVE-IT and other outcome trials with ezetimibe should have a careful look at this somewhat unexpected co-incidence of genetic cholesterol lowering by *NPC1L1* loss-of-function variants and gallstone formation.

Balance on a wider scale

More than a decade of intensive pharmacological research has brought hardly any newcomers with proven efficacy in preventing atherosclerosis to the market place. So what can we learn for preventive medication from genetic variants at the *NPC1L1* locus or, in more general terms, from the genetics of atherosclerosis?

First, genetics may guide pharmacological interventions to relevant mechanisms. A plethora of biomarkers showed association with atherosclerosis or other chronic disorders such that it is key to sort out factors which are causally involved rather than being innocent

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

[†] doi:10.1093/eurheartj/ehv108.

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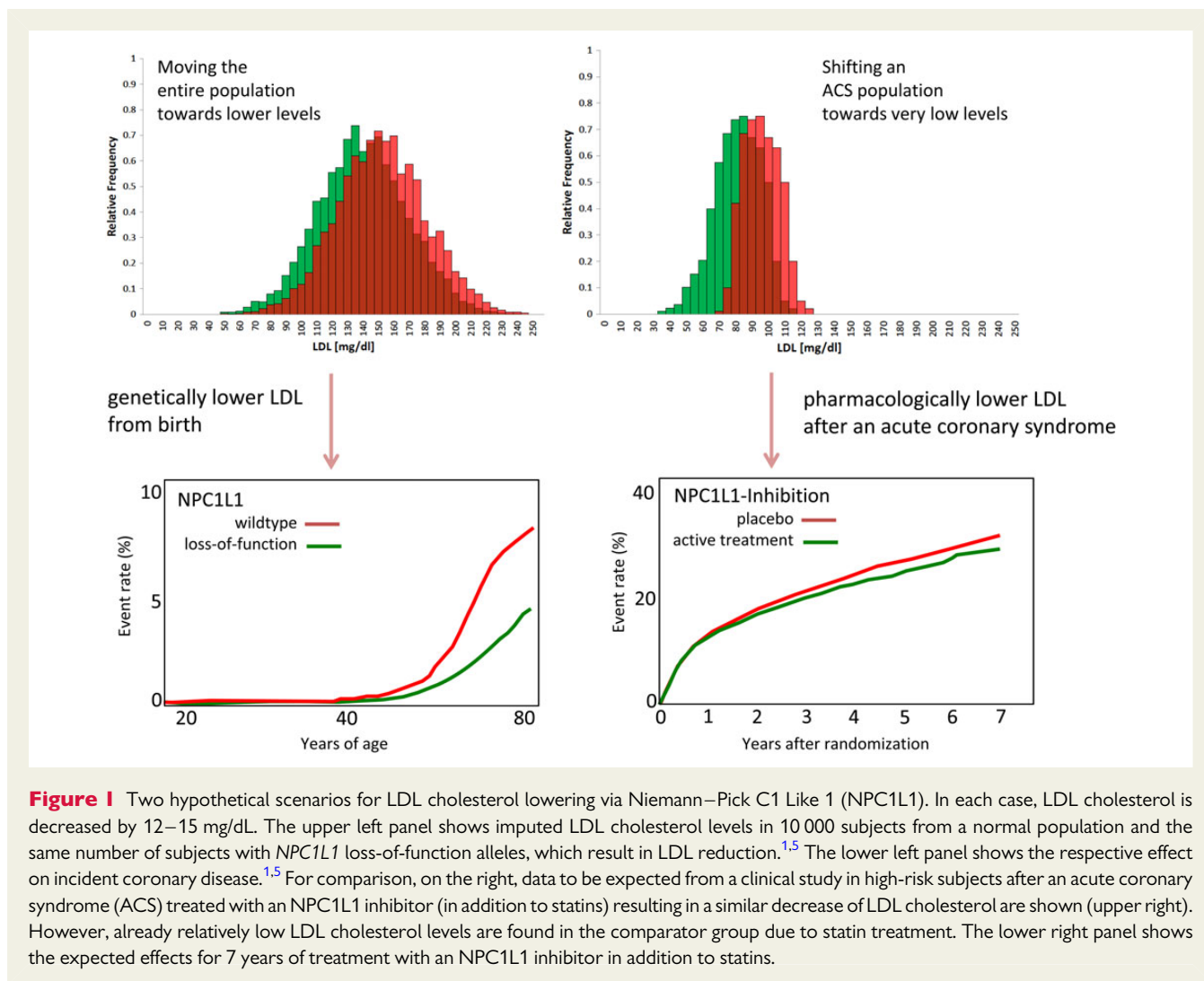


Figure 1 Two hypothetical scenarios for LDL cholesterol lowering via Niemann–Pick C1 Like 1 (NPC1L1). In each case, LDL cholesterol is decreased by 12–15 mg/dL. The upper left panel shows imputed LDL cholesterol levels in 10 000 subjects from a normal population and the same number of subjects with *NPC1L1* loss-of-function alleles, which result in LDL reduction.^{1,5} The lower left panel shows the respective effect on incident coronary disease.^{1,5} For comparison, on the right, data to be expected from a clinical study in high-risk subjects after an acute coronary syndrome (ACS) treated with an NPC1L1 inhibitor (in addition to statins) resulting in a similar decrease of LDL cholesterol are shown (upper right). However, already relatively low LDL cholesterol levels are found in the comparator group due to statin treatment. The lower right panel shows the expected effects for 7 years of treatment with an NPC1L1 inhibitor in addition to statins.

bystanders. This is the enormous advantage of genetic association studies.² Since alleles are randomly distributed in a population, their association with disease outcomes cannot be explained entirely by confounders, i.e. the genetically modified mechanisms are not only associated but need to be part of the disease process. The case of NPC1L1 may be a good example. Genetic studies may guide the way to the right target (or, as in the case of NPC1L1, put doubts about an established target to rest). If a mechanism offers opportunities for functional neutralization—as in the case of NPC1L1 via medical lowering of LDL cholesterol—it may be well suited for intervention.

At the same time, genetic variants may provide hints of potential risks for interfering with a given target. In fact, any drug needs to be safe in the first place. If a genetic variant goes along with a decreased risk for atherosclerosis, but an increased risk of some other critical disease, medical intervention addressing the same mechanism is likely to share these risks and may therefore be rendered unsuitable for preventive therapy. In this sense the example of NPC1L1 reminds us that any long-term treatment interferes with the balance in a biological system. With respect to medical treatment,

careful clinical testing in appropriately powered outcome studies and post-marketing surveillance need to address these concerns. Ultimately, it will be important to understand how far one can go in manipulating biology without causing unintended side effects.

Furthermore, NPC1L1 illustrates that causality may not always be as straightforward as it appears at first sight. Indeed, cholesterol is not the only molecule shuttled by NPC1L1. Rather, NPC1L1 and ABCG8, which showed a similar profile in the work of Lauridsen *et al.*,^{1,9} also transport phytosterols, which have been implicated in coronary artery disease risk before.^{9,10} Thus, the cargo of NPC1L1 or ABCG8, linking genetic variants and complex phenotypes, might be more diverse than suggested in the Mendelian randomization study.^{1,10}

Genetically guided fine-tuning of the balance: the future

An important finding of Lauridsen *et al.* as well as of previous studies^{5,6} is the fact that genetic variants may have by far larger

biological effects on complex phenotypes, i.e. ischaemic vascular events, than what would be expected given their immediate effects on intermediary phenotypes, i.e. LDL cholesterol or blood pressure.^{11,12} A possible explanation for this discrepancy may be that genetic variants take effect from birth (or even before) whereas medical therapy kicks in only after an initial manifestation of disease.

Lauridsen *et al.* speculate that the LDL lowering achieved in IMPROVE-IT would need to be maintained for ~18 years to achieve the same relative benefit as the genetic variants tested in their study.¹ Similarly, Ference and co-workers reported a two- to three-fold stronger risk decrease for genetically (lifelong) as compared with medically mediated reduction of LDL cholesterol as observed in clinical studies.¹¹ Thus, in addition to the individual level of LDL cholesterol, the length of its exposure seems to be of critical importance. This may challenge our current concepts of LDL reduction for prevention of cardiovascular events. Rather than going to lower and lower targets in high-risk populations one may ask for treatment even before any disease manifestation. Of course, selecting the right patient for such long-term treatment may be a challenge. After all, only 8% of individuals developed ischaemic vascular disease in the large population sample followed by Lauridsen *et al.* for >35 years.¹ Nevertheless, the genetic data strongly suggest that even small but chronic differences in LDL levels lead to sizeable traces in the risk profile. Accordingly, neutralization of such exposures should start early.

I want to end this Editorial with two further conclusions from the genetics of atherosclerosis. NPC1L1 represents only one of >60 chromosomal loci that carry variants affecting risk of coronary disease with genome-wide significance. About a quarter of these are linked to lipid metabolism. Thus, if we want to neutralize risk altogether, it will be necessary to interfere with further causal mechanisms in a way currently available by lowering LDL cholesterol.^{13,14} Secondly, in each of the currently known 60 plus risk loci for coronary disease one allele also carries—in a yin and yang mode—a non-risk allele. Thus, one may conclude that it is safe to interfere with many of the underlying pathogenic mechanisms as long as the fine-tuning does not challenge the overall balance of a biological system, and leads to gallstones or something similar.

Acknowledgements

I wish to thank Dr Felix Bourier for his help with the figure.

Conflict of interest: H.S. has received a grant from CADgenomics (Leducq Foundation), and honoraria from AstraZeneca, Servier, Boehringer-Ingelheim Pharma, MSD Sharpe & Dohme, Berlin-Chemie, and Amgen.

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