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The emerging concept of "individualized cholesterol-lowering therapy": A change in paradigm

Dieter Lütjohann [a], Frans Stellaard [a], Monique T. Mulder [b], Eric J.G. Sijbrands [b], Oliver Weingärtner [c,*]

[a] Institute of Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn, Bonn, Germany
[b] Department of Internal Medicine, Section of Pharmacology Vascular and Metabolic Diseases, Cardiovascular Research School COEUR, Erasmus Medical Center, Rotterdam, The Netherlands
[c] Klinik für Innere Medizin I, Universitätsklinikum Jena, Jena, Germany

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ABSTRACT

High LDL-cholesterol concentrations constitute a risk for atherosclerotic cardiovascular disease. By consensus, cholesterol-lowering therapy is initiated with a statin that reduces endogenous cholesterol synthesis, upregulates hepatic LDL receptor activity, increases LDL clearance and lowers LDL-cholesterol concentrations in the bloodstream. The efficacy of statin treatment is dose dependent and achieves a risk reduction of up to 50%. However, a substantial body of evidence suggests that a quarter of statin-treated patients do not respond adequately as a result of low endogenous cholesterol synthesis. In humans fractional cholesterol absorption varies from 20% to 80%. High cholesterol absorbers, which are characterized by a low-to-normal cholesterol synthesis, exhibit poor responsiveness to statin treatment. On the other hand, the cholesterol absorption inhibitor ezetimibe effectively reduces serum cholesterol levels in these patients. On this background, we suggest to "get personal" and individualize cholesterol-lowering therapies, according to the individual's status of cholesterol synthesis and absorption.

Contents

1. Introduction

Elevated serum cholesterol levels have been shown to be an independent risk factor for coronary heart disease (Castelli, 1984). The introduction of statins in the 1980s was a revolution in the treatment of hypercholesterolemia (Endo, 2008). Absolute risk reduction depends on serum cholesterol levels prior to treatment, the untreated cardiovascular disease risk, the magnitude of cholesterol reduction and the time point for the start of treatment. Large-scale primary and secondary prevention trials with statins have demonstrated a marked reduction in cardiovascular morbidity and mortality (Shepherd et al., 1995). One mmol/L (38.7 mg/dl) reduction inserum cholesterol reduces cardiovascular risk by 22% (Baigent et al., 2005). Nonetheless, meta-analysis of the statin trials point at a considerable residual cardiovascular risk in statin-treated patients (Heart Protection Study Collaborative, 2002). Inadequate cholesterol-lowering in patients on statins clearly contributes to this residual cardiovascular disease risk (Boekholdt et al., 2014).

Cholesterol is provided either by the diet (about 20%) or by endogenous synthesis in potentially all cells of the body (about 80%) (Cohen,

Abbreviations: ABCG5/G8, adenosine triphosphate binding cassette tandem transporter G5/G8; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein cholesterol; NPC1L1, Niemann-Pick C1-like 1 protein.

* Corresponding author.
E-mail address: Oliver.Weingaertner@med.uni-jena.de (O. Weingärtner).

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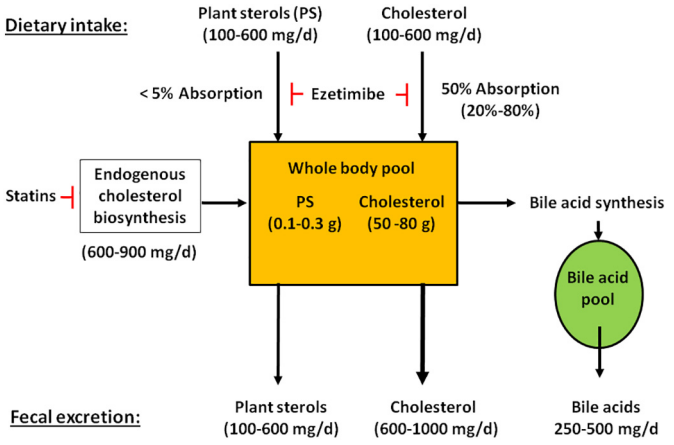

Fig. 1. Schematic overview of cholesterol metabolism in the human body. The daily dietary intake of cholesterol and phytosterols varies between 100 and 600 mg each (Nestel, Whyte, & Goodman, 1969; Wang, 2007). Bile acids are metabolites derived from cholesterol only and are essential for sterol and fat absorption. Together with cholesterol, plant sterols are secreted by the liver via the bile and efficiently absorbed from the distal small intestine. Isotope techniques and fecal excretion measurements have shown that, in healthy subjects, the fractional absorption rates vary from very low for phytosterols (<5%) to very high for bile acids (around 95%). In the same subjects, the fractional absorption rate for cholesterol itself averages 50% and is extremely variable from approximately 20–80% (Bosner et al., 1993; Bosner, Lange, Stenson, & Ostlund Jr., 1999). Ezetimibe inhibits the absorption of cholesterol and plant sterols by blocking the Niemann-Pick C1-like 1 (NPC1L1) sterol transporter protein at the apical membrane of enterocytes and the canalicular membrane of the hepatocytes (Altmann et al., 2004; Jia, Betters, & Yu, 2011). Cholesterol synthesis in humans occurs predominantly in extrahepatic organs, with a substantial contribution from the intestine (Dietschy, 1984; Dietschy & Gamel, 1971; Dietschy, Turley, & Spady, 1993). The liver is thought to contribute 10% to the whole body diurnal cholesterol synthesis, the intestines about 15% and other extra-hepatic organs the remaining part (van der Wulp, Verkade, & Groen, 2013). The total endogenous synthesis of cholesterol with a daily rate of 600–900 mg/d is thought to contribute about 60–80% of the total body cholesterol input. The 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) inhibit cholesterol synthesis and upregulate hepatic LDL receptors followed by reduction of blood levels of LDL-cholesterol. Cholesterol absorption, synthesis and secretion are well balance, which results in a body cholesterol pool varying between 50 and 60 g, while plant sterol uptake and fecal excretion (100–600 mg/d) stabilizes a whole body pool of about 0.1–0.3 g.

2008; Wang, 2007) (Fig. 1). Both endogenous cholesterol synthesis and intestinal cholesterol absorption regulate total serum cholesterol levels (Weingärtner, Lütjohann, Böhm, & Laufs, 2010). Humans with high cholesterol synthesis exhibit adequate low-density lipoprotein-cholesterol (LDL-C) reduction on statins, whereas those with high cholesterol absorption are characterized by suboptimal LDL-C reduction (Farnier et al., 2009; Gylling & Miettinen, 2002; Teoh et al., 2009; Thuluva et al., 2005). Notably, the inhibition of cholesterol synthesis increases both cholesterol and phytosterol absorption (van Himbergen et al., 2009). Phytosterols are structural homologues to cholesterol, which are of plant and dietary origin. The main representatives are campesterol and sitosterol and their blood levels reflect cholesterol absorption rates.

Table 1
Key messages.

- 25% of statin treated patients exhibit inadequate LDL-C lowering.
- Inadequate LDL-C lowering on statin treatment is observed in patients with low cholesterol synthesis and high cholesterol absorption.
- Ezetimibe lowers LDL-C effectively when cholesterol absorption is high and cholesterol synthesis is low.
- LDL cholesterol lowering therapy should be personalized to meet individual patient requirements in terms of cholesterol synthesis and absorption.
- Markers of cholesterol absorption (e.g. campesterol) and markers of cholesterol synthesis (e.g lathosterols) have to be determined before and during therapy to optimize LDL-C lowering effectiveness.

The efficacy of inhibition of cholesterol synthesis by statins, but also the efficacy of inhibition of cholesterol absorption by ezetimibe, may have been underestimated as a substantial proportion of the patients in the reported trials were poor or non-responders to therapy based on individual genetic patterns in their metabolic background.

In this review, we summarize results from retrospective clinical trials which demonstrate that markers of cholesterol metabolism - such as serum lathosterol (synthesis marker) and campesterol or cholestanol (absorption marker) - are associated with cardiovascular risk. Prospective clinical trials reveal individual differences in efficacy in response to cholesterol-lowering drugs. And most importantly, results from prospective, randomized-controlled trials suggest that markers of cholesterol metabolism can be used to determine which patient will benefits the most from high intensity statin treatment and which patients will benefit instead from "dual cholesterol-lowering therapy" with a statin and a cholesterol absorption inhibitor.

2. The concept of individualized cholesterol-lowering therapy

For a large group of patients, cholesterol-lowering attempts end up in laborious trial and error routes ever since the novel LDL-C lowering drugs came onto the market. For example, 40 mg daily of atorvastatin reduces LDL-C in patient A by 15%, but in patient B by 50%. Due to differences in cholesterol metabolism patient A is a suspected "high cholesterol absorber" and therefore a "poor responder" to statin therapy, whereas patient B as a "high cholesterol synthesizer" exhibits adequate LDL-C lowering on atorvastatin therapy. Patient A will benefit from "dual cholesterol-lowering therapy" with a statin and ezetimibe, whereas patient B, as a high cholesterol synthesizer, is a candidate for high intensity statin monotherapy.

In this review, we propose a change in paradigm for cholesterol-lowering therapy and consider markers of cholesterol absorption to individualize the initial choice of cholesterol- lowering treatment. If we are able to treat more patients optimally with the first lines of treatment (statins and ezetimibe), the selection of patients in need of the novel cholesterol-lowering drugs (anti-PCSK9 antibodies, mipomersen, and lomitapide) will become more accurate as well.

Early results from the landmark statin trial "4S" demonstrated, that patients with high baseline cholesterol absorption did not benefit from statin treatment (Miettinen, Gylling, Strandberg, & Sarna, 1998). On the contrary, patients with high cholesterol absorption were

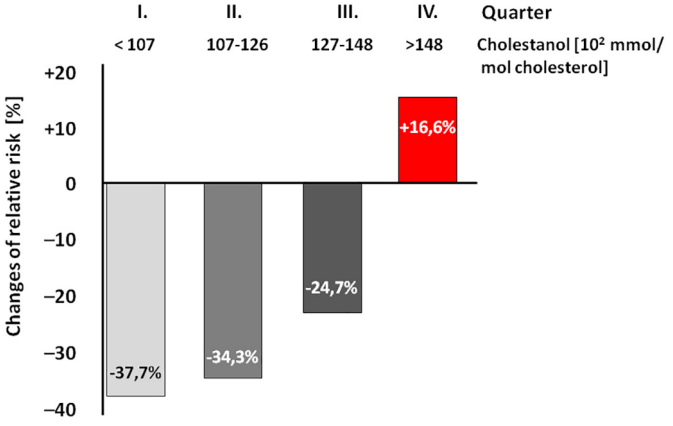

Fig. 2. The 4S subgroup evaluation. Cholesterol hyperabsorbers are characterized by increased major coronary events, including coronary deaths, non-fatal myocardial infarctions, and revascularization procedures. Changes in relative risk of major coronary events by simvastatin in patients from the Finnish subgroup of the Scandinavian simvastatin survival study were defined by baseline quarters of proportion of the ratio of cholestanol to cholesterol, the 5α-saturated metabolite of cholesterol and an additional surrogate serum marker of cholesterol absorption (Miettinen et al., 1998). The higher the quarter of the serum cholestanol ratio was the greater the risk of major coronary events. This figure was established from data given in Table 1 in (Miettinen et al., 1998).

characterized by a 16.6% increase in cardiovascular events on statin monotherapy (Fig. 2). Miettinen and colleagues concluded, that patients with high baseline cholesterol synthesis are responders to statin therapy whereas, on the other hand, patients with high cholesterol absorption are non- or "adverse"-responders. Results of cholesterol-lowering trials throughout the last three decades reaffirm the early findings by Miettinen et al. (1998) that roughly a quarter of patients on statin monotherapy do not benefit from statin monotherapy, but need an additional cholesterol absorption inhibitor. These findings inevitably lead to the idea of "individualizing cholesterol-lowering therapy" guided by differences in cholesterol metabolism (Miettinen et al., 1998; Weingärtner, Lütjohann, Böhm, & Laufs, 2011). This emerging concept is further supported by results from recently published genetic association studies. In line with this evidence, proxies of cholesterol absorption and synthesis and a strategy with a detailed genetic analysis of cholesterol homeostasis-regulating genes might be required to optimize cholesterol-lowering therapy.

2.1. Genetics and cholesterol metabolism

Genetic studies demonstrate that a life-long reduction of serum cholesterol levels by one mmol/L (38.7 mg/dL) reduces cardiovascular disease risk by 22% (Ference et al., 2012). Recently, Stitziel et al. (2014) confirmed with a Mendelian randomization method that inactivating mutations of *NPC1L1* led to an impressive cardiovascular risk reduction. Heterozygotes for an inactivating mutation of *NPC1L1* - a transport protein essential for cholesterol absorption (Fig. 3) - exhibited a minor decrease of 12 mg/dL serum cholesterol, but a dramatic 53% reduction of cardiovascular risk. Moreover, Teupser and colleagues reported that the sterol transporter gene *ABCG8* - a transport protein essential for the efflux of plant sterols from the enterocyte back into the gut -*is directly related to serum phytosterol levels and cardiovascular risk in the general population* (*Teupser et al. 2010*), similar to patients suffering from sitosterolemia (Lee et al., 2001; Sudhop, Lütjohann, & von Bergmann, 2005; Sudhop & von Bergmann, 2004). The results from these two independent genetic studies support the notion that inactivating mutations of either *NPC1L1* or *ABCG8* have a strong impact on cardiovascular risk, which is independent from serum cholesterol levels. (Weingärtner, Lütjohann, & Patel, 2015).

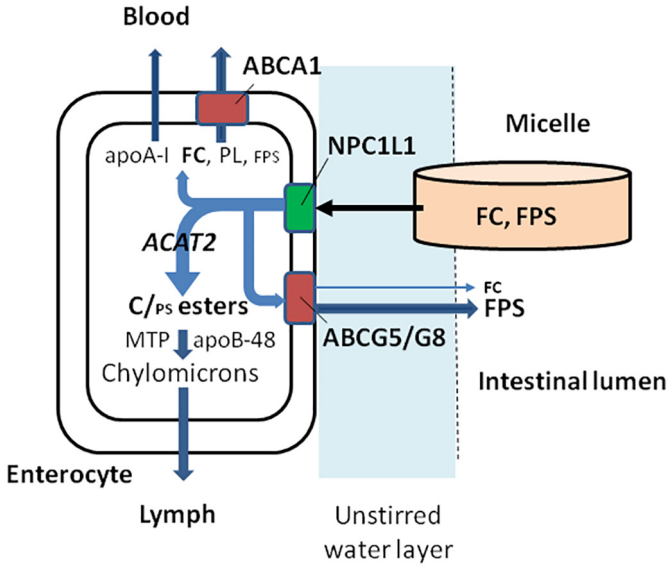

Fig. 3. Sterol uptake within the intestine. Emulsification of dietary sterols and fats leads to stable, well-dispersed micro fat droplets that allow access to hydrolyzing enzymes to convert triglycerides into free fatty acids and monoacylglycerols, phospholipids into lysophospholipids and sterol esters into free sterols (Kohlwein, Veenhuis, & van der Klei, 2013). The hydrolysis products together with bile salts form mixed micelles. In this way, the water-insoluble compounds are transported down the small intestine and delivered to the enterocytes for absorption (Hofmann & Hagey, 2014). Free fatty acids, monoacylglycerides and lysophospholipids, free cholesterol (FC) and free phytosterols (FPS) are transported through the unstirred water layer to the enterocyte mucosa. The sterol transporter Niemann-Pick C1-like 1 protein (NPC1L1) transfers sterols into the enterocyte. Most of the FPS (98%) and a minor part of FC are re-secreted into the intestinal lumen by the ABCG5/G8 tandem transporter into the intestinal lumen. Fatty acids and monoglycerides are re-esterified to triglycerides, lysophospholipids converted to phospholipids (PL), and sterols, mainly cholesterol to sterol esters by cytosolic acetyl-CoA acetyltransferase type 2 (ACAT2). Microsomal triglyceride transfer protein (MTP) catalyzes transport and insertion of these compounds into newly formed chylomicrons, which are secreted into the lymph. Apo-AI together with FC and PL are transported by the ABC sub-family A1 (ABCA1) transporter protein into the blood. The lipid-poor Apo-AI (pre-β1-HDL) together with FC and PL forms nascent, discoidal HDL (D'Aquila, Hung, Carreiro, & Buhman, 2016; Iqbal, Anwar, & Hussain, 2003; Iqbal & Hussain, 2005; März et al., 2017). ApoB-48, apolipoprotein B-48.

2.2. Markers of cholesterol metabolism and the association with cardiovascular risk

Silbernagel et al. (2009, 2010) demonstrated that high cholesterol absorption and low cholesterol synthesis in the LURIC-study is associated with coronary heart diseases and cardiovascular mortality. Moreover, results from a small cohort study from our group demonstrated that the ratio of campesterol to lathosterol (high cholesterol absorption and low cholesterol synthesis) was directly associated with the degree of coronary heart disease and was a strong independent predictor for concomitant coronary heart disease (Weingärtner et al., 2009). These findings were reaffirmed in the Framingham-offspring-study in which the ratio of campesterol to lathosterol was similarly related to cardiovascular risk. In that study Matthan et al. (2009) concluded that "cholesterol homeostasis markers appear to be better predictors of disease than traditional lipid risk factors". In another prospective cohort study of patients undergoing coronary angiography the oxidized plant sterol 7β-hydroxycampesterol was associated with cardiovascular events (Fuhrmann et al., 2018).

2.3. Markers of cholesterol metabolism, renal impairment and diabetes mellitus

In hemodialysis patients, statins have failed to reduce hard cardiovascular endpoints (Baigent et al., 2011; Fellstrom et al., 2009; Wanner et al., 2005). In the 4D study, 20 mg atorvastatin reduced LDL-C, but was not superior to placebo with regard to reduction of hard cardiovascular endpoints (Krane et al., 2008). Moreover, 10 mg rosuvastatin failed to show an effect on this composite endpoint in the AURORA study (Holdaas et al., 2011). A small prospective study from our group put these results in a new perspective. Patients on hemodialysis - in contrast to patients without impaired renal function - are characterized by high cholesterol absorption and reduced cholesterol synthesis (Rogacev et al., 2012). In this cohort of patients at high cardiovascular risk, half of the patients died after a follow-up period of four years. These findings offer a potential explanation for the results of the SHARP study. In contrast to AURORA and 4-D, SHARP resulted in a positive outcome for combined cholesterol-lowering in patients with at least stage three chronic impaired renal function (Baigent et al., 2011). Of note, in SHARP, LDL-C reduction was only 31%, whereas in AURORA LDL-C reduction was 41%. Finally, a post hoc- analysis of the AUROA study by Silbernagel et al. (2015) further supports our concept. Statin monotherapy reduced cardiovascular endpoints only in the subset of patients with high cholesterol synthesis, but not in those with high cholesterol absorption. Of note, again, a quarter of the study population in AURORA showed a benefit from the individualized treatment approach. Therefore, we suggest to consider these findings in future cholesterol-lowering guidelines and recommend "dual cholesterol-lowering therapy" with a statin and a cholesterol absorption inhibitor in patients with renal impairment.

Moreover, the findings of high cholesterol absorption and low cholesterol synthesis, as indicated by serum non-cholesterol sterols, in

patients with type 1 diabetes suggested that the variables of cholesterol metabolism are opposite to those in type 2 diabetes (Miettinen, Gylling, Tuominen, Simonen, & Koivisto, 2004). Therefore, patients with type 1 diabetes benefit more from "dual cholesterol-lowering therapy" with a statin and a cholesterol absorption inhibitor. In an elegant cross-over study, Ciriacks, Coly, Krishnaswami, Patel, and Kidambi (2015) assigned subjects with type 1 or type 2 diabetes mellitus to alternating therapy with 40 mg simvastatin or 10 mg ezetimibe daily for six weeks. Interestingly, inhibition of cholesterol synthesis was less effective in patients with type 1 diabetes, whereas cholesterol absorption inhibition was less effective in patients with type 2 diabetes. We therefore urge that in addition to prospective clinical trials evaluating these findings, hard cardiovascular outcome trials such as IMPROVE-IT and HIJ-Proper should reevaluate treatment efficacy in patients with diabetes mellitus, differentiating between type 1 and type 2 diabetes.

2.4. Cholesterol metabolism and coronary atherosclerotic lesions

A number of well-performed trials investigated the effect of cholesterol-lowering therapies on coronary atherosclerotic lesion development by using intravascular ultrasound (IVUS) or optical coherence tomography (OCT), and they provide further evidence of the benefits of a personalized approach to lowering blood lipids. A Japanese group analyzed the extent of coronary heart disease in patients not on lipid lowering drugs by using OCT (Nasu et al., 2013). In this study, patients with thin cap fibrous atheroma were characterized by a high ratio of campesterol to lathosterol. The ratio of campesterol to lathosterol, LDL-cholesterol and high-sensitive C-reactive protein (CRP) were positively correlated with the necrotic core of coronary atherosclerotic plaques. Moreover, Nasu et al. (2013) demonstrated that the ratio of campesterol to lathosterol - meaning previous life-long high cholesterol absorption and low endogenous cholesterol synthesis - was the strongest predictor of a thin cap coronary atherosclerotic lesion. The authors concluded that differences in cholesterol metabolism were directly associated with the "vulnerability" of atherosclerotic plaques. These findings are of particular interest, since the positive outcome of the IMPROVE-IT trail was driven solely by acute myocardial infarction and stroke - acute incidences of atherosclerotic plaque rupture - a finding with the pathophysiological basis of atherosclerotic lesions with rather thin caps and large lipid cores (Bohula et al., 2017; Cannon et al., 2015; Eisen et al., 2016; Giugliano et al., 2018). In another study using IVUS in 647 consecutive patients with stable coronary artery disease similar results were demonstrated by Kataoka et al. (2015). After 12 months on statin monotherapy approximately a quarter of the patients - comparable to the early subgroup analysis of 4S study by Miettinen et al. (1998) - had an inadequate cholesterol-lowering response to statin monotherapy. Interestingly, these patients were characterized by rapid atherosclerotic plaque volume progression on IVUS follow-up. Having the concept of "individualized cholesterol-lowering therapy" in mind, we asked Kataoka et al. to allow us to determine cholesterol homeostasis markers in this study, to verify that patients who respond ineffectively to statin treatment are characterized by high cholesterol absorption and low endogenous cholesterol synthesis (Weingärtner, Lütjohann, Plösch, & Elsässer, 2017). It is tempting to speculate that this subgroup of patients would benefit in particular from adding a cholesterol absorption inhibitor. This approach should be further tested by a prospective follow-up study in this cohort.

Finally, the results of the PRECISE-IVUS-study further add to this notion. In this study 202 patients with stable angina pectoris or acute coronary syndrome were investigated with IVUS at baseline and at follow-up on either atorvastatin monotherapy (LDL-goal of 70 mg/dl) or a combination therapy with ezetimibe and atorvastatin (Tsujita et al., 2015). After a follow-up period of 9–12 months patients on statin monotherapy achieved a mean LDL-C of 73.2 mg/dl, whereas patients on the combination therapy achieved an LDL-C of 63.3 mg/dl. Interestingly, the analysis by IVUS at follow-up demonstrated a significant

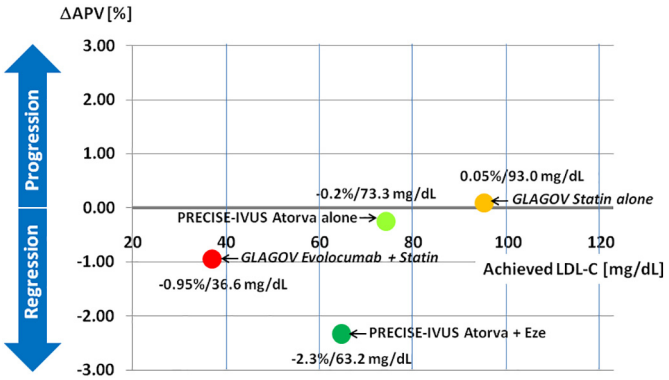

Fig. 4. Comparison of the relationship between achieved LDL-C levels and the median change percent atheroma volume (PAV) for the PRECISE-IVUS and the GLAGOV-trial. PRECISE-IVUS study (Tsujita et al., 2015): The treatment with the combination of atorvastatin and ezetimibe for 9–12 months resulted in lower levels of LDL-C than atorvastatin monotherapy (63.2 ± 16.3 mg/dl vs. 73.3 ± 20.3 mg/dl; $p < .001$). Compared with standard statin monotherapy, the combination of statin plus ezetimibe showed greater coronary plaque regression in patients with acute coronary syndrome compared with statin monotherapy (absolute change in percent atheroma volume: −2.3% vs. −0.2%; $P < .001$), which might be attributed to cholesterol absorption inhibition-induced aggressive cholesterol-lowering. GLAGOV study (Nicholls et al., 2016): Compared with placebo, the evolocumab group achieved lower mean LDL-C levels (93.0 vs 36.6 mg/dL; $P < .001$) after 48 weeks. The primary efficacy parameter, PAV, increased 0.05% with placebo and decreased 0.95% with evolocumab ($P < .001$). The combination therapy atorvastatin and ezetimibe in PRECISE-IVUS demonstrated the most pronounced effect on lesion regression. This effect outweights the effect of adding a PCSK9-inhibotor in the GLAGOV-trial, which lowered LDL-C more effectively, and further supports the importance of additional inhibition of cholesterol absorption.

reduction of atherosclerotic lesions with combined cholesterol-lowering therapy compared to statin monotherapy. The greatest effect was observed in patients with acute coronary syndromes. The authors speculated that combined cholesterol-lowering therapy may be more effective than statin monotherapy especially in patients with acute coronary syndromes. In our opinion, these findings are based on a selection of high cholesterol absorbers in this group. In case future prospective studies demonstrate similar findings, combined cholesterol-lowering therapy should be considered in all patients with acute coronary syndromes (Nasu et al., 2013).

Most interestingly, however, when comparing all known IVUS studies that are evaluating cholesterol-lowering therapies, the combination therapy with a statin and ezetimibe in PRECICE–IVUS demonstrated the most pronounced effect on lesion regression (Tsujita et al., 2015) (Fig. 4). This effect outweighs the effect of an additional PCSK9-inhibitor in the GLAGOV trial, which reduced LDL-C more effectively (Nicholls et al., 2016) and further supports the paramount importance of additional inhibition of cholesterol absorption. These findings are all the more important, because the combination of a statin and ezetimibe is far more cost effective than the combination of a statin and a PCSK9-inhibitor.

There are also studies that do not support our concept. The ENHANCE-trial was performed in statin-treated patients with heterozygous familial hypercholesterolemia (Kastelein et al., 2008). Prior to study inclusion, the majority of these patients had been on long term high intensity statin treatment and had normal carotid intima media thickness at baseline. Therefore, no improvement on the combinatory therapy simvastatin plus ezetimibe vs. statin monotherapy could be found. In a recent investigation using direct indices of drug action and compliance, Lakoski et al. (2010) found no explanation for differences in response among individuals on statins or ezetimibe with differences in compliance or indices of cholesterol absorption or synthesis using serum surrogate markers. However, this study was restricted to a subset of 40% African-Americans and only men with mild to moderate hypercholesterolemia and to a small sample size combined with low-dose regimens.

As early as 1990, results from the POSCH-study have demonstrated for the first time that "hard cardiovascular endpoints" can be significantly reduced by lowering of cholesterol absorption through a surgical shortening of the intestine Buchwald et al., 1990. The availability of pharmacological approaches to inhibit cholesterol absorption made this concept much more appealing. The IMPROVE-IT-study is the landmark study in which cholesterol absorption inhibition via NPC1L1 resulted in a reduction of the composite clinical endpoint of myocardial infarction and ischemic stroke (Giugliano et al., 2018).

A subgroup-analysis of the IMPROVE-IT study further adds to the notion of individualizing cholesterol-lowering therapy. In general the number needed to treat with a combination of a statin and ezetimibe vs. statin monotherapy, improved directly with the increase of the patients' cardiovascular risk at study baseline (Bohula et al., 2017; Giugliano et al., 2018). Patients after bypass-surgery showed the greatest benefit. But similar effects on hard cardiovascular outcomes were reported for ischemic stroke. In patients with prior ischemic stroke a combined cholesterol-lowering with ezetimibe and simvastatin resulted in a dramatic risk reduction compared to statin-monotherapy (Bohula et al., 2017) with a number needed to treat of 19. Interestingly, we have previously demonstrated in mice, using the reversed reasoning that plant sterol supplementation - plant sterol uptake is also inhibited by ezetimibe - results in greater ischemic stroke size and endothelial dysfunction (Weingärtner et al., 2008). Moreover, findings in a recently published small clinical study revealed that patients with ischemic stroke exhibit higher levels of plant sterols compared to controls (Sivrikaya et al., 2018). Therefore, patients with ischemic stroke, especially those with a previous history of ischemic stroke, benefit in particular from combined cholesterol-lowering, a finding that should also be addressed in future cholesterol-lowering guidelines.

Most importantly, the recently published HIJ-Proper-study provided evidence for an individualized approach to cholesterol-lowering therapy (Yamaguchi et al., 2018). Combined cholesterol-lowering with pitavastatin and ezetimibe reduced cardiovascular events only in patients, who had high serum sitosterol levels, whereas patients with low sitosterol levels (low cholesterol absorption) did not benefit from combined lipid lowering therapy. The authors correctly concluded that sitosterol measurement in patients with acute coronary syndrome might contribute to a personalized cholesterol-lowering approach.

Taken together, there is accumulating evidence for determining the balance of cholesterol absorption and cholesterol synthesis prior to the start of cholesterol-lowering treatment. There is an urgent need for a large scale implementation study to identify the best predictors of cholesterol metabolism to tailor cholesterol-lowering therapy on an individual basis. Measurement of campesterol, sitosterol, cholestanol and lathosterol will enable to select the combination or ratio of markers with the highest discriminative ability.

Alternatively, a detailed genetic analysis of cholesterol homeostatis should be performed to test the strategy on the basis of Mendelian randomization to optimize cholesterol-lowering therapy. Finally, health economic issues as well as cost-effectiveness will have to be addressed. Both mass spectrometry for analysis of serum non-cholesterol sterols and genetic testing offer high-throughput at decreasing costs. Large scale application will result in prices that are not different from the costs of measuring a simple lipid profile.

3. Conclusion and future perspectives

LDL cholesterol-lowering therapy is essential for cardiovascular risk reduction. On the background of a high inter-personal variation of cholesterol synthesis and cholesterol absorption the efficacy of cholesterol lowering, both, with statins and with ezetimibe exhibits a wide variation. Bempedoic acid, which reduces cholesterol synthesis through inhibition of adenosine triphosphate citrate lyase, an enzyme upstream from 3-hydroxy-3-methylglutaryl-coenzyme A, may provide an oral therapeutic option complementary to ezetimibe in statin-intolerant patients who require additional LDL-C lowering (Ruscica, Banach, Sahebkar, Corsini, & Sirtori, 2019). The determination of markers of cholesterol metabolism offers the unique opportunity to get a more detailed understanding of the individual patient. Therefore, future clinicians will need to "get personal" in their counseling and prescription of cholesterol-lowering agents to become more effective in the prevention of cardiovascular disease progression. Future approaches call for "individualized" concepts in lipidology. To establish these concepts, individual differences in cholesterol metabolism and their effects on different cholesterol-lowering strategies deserve increased scrutiny and investigation.

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Conflicts of interest statement

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