ESC Position Paper on statins adherence and implementation of new lipid-lowering medications: barriers to be overcome

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Abstract

Benefits and safety on statins have been well established over 20 years of research. Despite this, the vast majority of patients are not adequately treated and do not achieve the low-density lipoprotein cholesterol target levels. This is mainly due to poor adherence, which is associated with dangerous and sometimes fatal outcomes.

To increase adherence and prevent worse outcomes, a combination therapy with lower dosage of statins and new lipid lowering drugs may be used. However, the implementation of new lipid lowering drugs in European countries is still at the beginning.

For these reasons, aim of this position paper is to give an up-to-date indication from the European Society of Cardiology in order to discuss the barriers towards statins adherence and new lipid lowering drugs implementation in Europe.

Key words:

Statins adherence; statin intolerance; low-density lipoprotein cholesterol; ezetimibe; PCSK9 inhibitors; position paper

Introduction

Statins have a documented efficacy in lowering low-density lipoprotein cholesterol (LDL-C) levels and, also, in improving primary and secondary cardiovascular endpoints. Benefits of statin treatment in cardiovascular and non-cardiovascular patients have been fully acknowledged (1-4). As such, statins have a Class 1A recommendation for hypercholesterolaemia according to the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias (4). In particular, statins should be prescribed to the highest therapeutic possible dose to reach the target level (5). Nevertheless, statin therapy initiation is challenging as high-dose statins are infrequently prescribed at discharge and use rates are even lower by one year after discharge (6). Thus, statins are underused and underdosed (7-8).
Also, adherence to guideline-recommended statin therapy is far from optimal, and LDL-C targets are not achieved in up to 80% of high-risk patients (9-12). Barriers to statin therapy implementation are shown in Figure 1. The main barrier is poor adherence to statin therapy, that is associated with a significantly increased risk of cardiovascular events and mortality. Statin intolerance is associated with an increased risk for recurrent myocardial infarction and coronary heart disease events (13).

Taking into account these issues, a multidisciplinary panel of leading international experts has been organised by the ESC to discuss the latest evidence, ongoing research and controversial issues regarding statins non-adherence and to discuss the barriers of implementation of new-lipid lowering drugs in Europe. This executive document reflects the key points of the ESC consensus meeting.

Definitions

Whilst the term "compliance" has been used historically to indicate a somewhat paternalistic view of the doctor-patient relationship ("The patient is simply to do what I tell to do.") (14), "adherence" to treatment is considered as the extent to which the patient continues an agreed-upon mode of treatment despite conflicting demands (8).

Adherence is therefore defined as the extent to which a patient's behaviour—taking medication or changing lifestyle—corresponds with agreed recommendations from a healthcare provider (15). Regarding taking medications, adherence is composed by at least three components: initiation of treatment, execution of treatment, and persistence of treatment over time (15). The last component, "persistence", refers to the act of continuing the treatment for the prescribed duration (8, 16). When non-adherence occurs at the beginning, it may imply poor acceptance and therefore non-initiation of the therapeutic plan. Delayed or omitted drug intake leads to poor execution. Finally, intermittent or permanent discontinuation leads to poor persistence (17).

Consequences of statins non adherence

Non adherence is the most important *modifiable* factor that compromises treatment outcomes (18) and has devastating clinical consequences. In outpatients with stable coronary heart disease (19), non-adherence was associated with a greater than two-fold increased rate of subsequent cardiovascular events, more than four times increased risk of stroke and almost a four-fold increased risk of death.

Accordingly, adherence to drug therapy may be a surrogate marker for overall healthy behavior. In fact, a meta-analysis showed that good adherence to placebo was associated with lower mortality, supporting the existence of the "healthy adherer" effect (20). Consistently, a study (21) showed that statin-adherent patients were half as likely to experience a subsequent myocardial infarction. In younger patients (<65 years) this reduction in myocardial infarction rates was even greater.

Largely due to increased hospitalisations, non adherence is also costly for the healthcare system. Thus, for all these reasons, monitoring and promoting adherence to statin therapy is a priority. A comprehensive approach is needed in order to increase statin adherence (8, 22).

Barriers for statins non adherence and possible solutions

Common factors leading to statin non adherence and suggested strategies are shown in table 1.

At the beginning of the treatment, if the patient shows unwillingness to start statin therapy, the clinician is recommended to provide counsel about the risks of myocardial infarction and stroke, in order to offer education and support to the patient. Indeed, misperception regarding the risks and benefits of statin treatment is a common factor of non adherence (23).

In the case of early discontinuation, a re-counseling should be provided as well. Of note, adherence to statin treatment drops over time, particularly when treating the asymptomatic patient. In fact, the most common pattern of non-adherence to statin therapy is observable at 1 month of treatment, when the target level is reached (8). At 6 months, nearly 50% of primary prevention patients have already stopped therapy (24). To prevent this pattern, it may be useful to schedule the re-counseling sessions (25, 26). Finally, since coronary events may occur, residual risk should be addressed in secondary prevention.

Therefore, to avoid discontinuation, educational support from the healthcare provider is suggested.

One of the principal reasons for statin discontinuation is myalgia (27). This is a serious and apparently common side effect of statins, affecting up to 25% of patients (27). In this case, the clinician is recommended to check for causality. Indeed, many of the self-reported muscle symptoms are not actually attributable to statins. This has been proven by clinical trials, suggesting that myalgia is also frequently reported in placebo groups (28). Thus, the presence of myalgia as a *nocebo* effect may be linked to patient's negative expectations due to knowledge of statin side-effects. The ongoing series of randomised controlled "N-of-1" trials comparing atorvastatin and placebo in UK primary care will help further elucidate this issue (29). As demonstrated by the ODYSSEY LONG TERM (Long-term Safety and Tolerability of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia) trial (30), side effects may not occur if patients are blind about treatment. This suggests that awareness of side effects, more than side effects themselves, may be a cause of discontinuation.

One approach is that patients should be unaware of muscle pain, to avoid discontinuation, and future guidelines should keep into account these considerations.

Of note, the panel agrees that "true" (i.e. cause-effect) correlation between muscle pain and statin use is very uncommon (1%) and that statin intolerance may be therefore a subjective phenomenon. As recently pointed out by the ESC working group on Cardiovascular Pharmacotherapy (8), and by further studies (31, 32), a minority of patients is truly statin intolerant.

When an established and documented link between statin therapy and myalgia is set, the clinician is asked to re-challenge with a second statin. If suspected statin intolerance is confirmed on statin rechallenge, achieving guideline-recommended LDL-C goals with other drugs than statins is indicated (8). Clinically relevant statin-related muscle symptoms should be proven with at least three different statins, so patients will be offered therapeutic regimens to adequately prevent their cardiovascular risk (27). If this approach is not successful, other combinations may be prescribed. However, many experts suggest to start the therapeutic plan with a combination therapy in order to avoid problems linked to therapeutic interchange, typically observed with a stepwise approach.

Combination therapy with new lipid lowering drugs: ezetimibe

Combination therapies present different advantages as elsewhere reviewed (33). First, they have a synergistic effect, thus the efficacy is thought to be higher compared to the sum of single drugs. Second, they have less adverse events and are therefore are better tolerated. Last but not least, the simplified drug regimen usually leads to better adherence and, potentially, better outcomes and costs reduction for the healthcare.

As shown by clinical trials (34-36), statins combined with ezetimibe, a nonstatin drug lowering intestinal cholesterol absorption, reduce LDL-C and cardiovascular events. For this reason, combination therapy with ezetimibe and statins is recommended if goals are not reached by statins alone.

Use of ezetimibe in patients who are not at target

The consensus panel debated on whether adding ezetimibe to statin in patients who are not at target allows to reach the target with no/ less adverse events (i.e. myalgia).

The ACTE (A Multicenter, Randomized, Double-Blind, Titration Study to Evaluate the Efficacy and Safety of Ezetimibe Added On to Rosuvastatin Versus Up Titration of Rosuvastatin in Patients With Hypercholesterolemia at Risk for Coronary Heart Disease) study (37) evaluated the safety and efficacy of ezetimibe added to stable rosuvastatin therapy versus up-titration of rosuvastatin in patients with hypercholesterolemia. The trial found that compared to up-titration of the rosuvastatin dose, ezetimibe 10 mg primarily added to stable rosuvastatin 5 mg or 10 mg produced greater improvements in lipid profile, with better achievement of the LDL-C goals.

Similarly, the I-ROSETTE (Ildong ROSuvastatin & ezETimibe for hypercholesTElolemia) trial (38) an 8-week, phase III, multicenter, randomised, double-blind, active comparator clinical trial, compared the efficacy and safety of several combinations with ezetimibe and rosuvastatin versus those of rosuvastatin monotherapy in patients with hypercholesterolemia. Patients were randomly assigned to receive ezetimibe 10 mg/rosuvastatin 20 mg, ezetimibe 10 mg/rosuvastatin 10 mg, ezetimibe 10 mg/rosuvastatin 5 mg, rosuvastatin 20 mg, rosuvastatin 10 mg, or rosuvastatin 5 mg. The study found that all the fixed-dose combinations of ezetimibe/rosuvastatin significantly improved lipid profiles in patients with hypercholesterolemia compared with rosuvastatin monotherapy. In particular, all groups treated with ezetimibe/rosuvastatin reported a decrease in mean LDL-C level >50% from baseline values. The safety and tolerability of ezetimibe/rosuvastatin therapy were comparable with those of rosuvastatin monotherapy.

These data have been confirmed also in non-ST elevation acute coronary syndrome by a randomised trial (39) investigating whether intermediate-intensity dosage statins combined with ezetimibe was superior to high-intensity statin monotherapy. The study found that the combination

of rosuvastatin 10mg/ezetimibe 10mg was superior to rosuvastatin 20mg or 10mg with a greater effect on lowering LDL-C and a lower incidence of drug-related adverse events.

Use of ezetimibe in high-risk patients

A question arises as for the use of add-on ezetimibe to statins in specific subgroups who are already at target, such as high risk patients or those with comorbidities. To this aim, the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) (40) investigated the efficacy of ezetimibe in patients stratified by TIMI (Thrombolysis In Myocardial Infarction) risk score, showing that high-risk patients had the greatest benefit from the addition of ezetimibe to statin therapy on the primary composite endpoint (cardiovascular death, myocardial infarction, stroke, hospital admission, and coronary revascularisation). Further, the benefit of adding ezetimibe to statin was shown to be greater in patients with diabetes mellitus and also, in high-risk patients without diabetes (41). No gender-related differences were observable in terms of benefits of adding ezetimibe to statin (42). Notably, patients achieving an LDL-C level less than 30 mg/dL at 1 month had the lowest rate of cardiovascular events over a 6-year period compared with patients achieving higher LDL-C levels, but with similar safety profiles (43). These results provide reassurance regarding the longer-term safety and efficacy of the further lowering of LDL-C concentrations below the standard 30 mg/dL level in higher-risk patients.

The consensus panel therefore agrees that data so far available support the use of intensive combination lipid-lowering therapy with ezetimibe and statin to improve cardiovascular outcomes, with a good safety profile, also in high-risk subgroups who are already at target. From these results, the panel suggests to stratify patients according to the risk and then lower LDL-C less than 30 mg/dL as a beneficial strategy in high risk patients.

Use of ezetimibe to improve adherence

The final question is whether there is advantage or not by using a fixed combination ezetimibe/statin therapy on patient adherence. We know that adherence decreases with increasing number of pills, and this may be common in patients after a coronary acute event. A retrospective study (44) in patients with concomitant antihypertensive and lipid-lowering therapy found a greater adherence in those initiating the two therapies together, suggesting that a fixed combination may improve adherence to treatment.

In conclusion, fixed combination ezetimibe/statin increases LDL-C control, reduces adverse effects and may also improve adherence, which is a major determinant of good outcomes.

Combination therapy with PCSK9 inhibitors

In patients with high risk for cardiovascular disease, the 2016 ESC/EAS guidelines (4) recommended treatment with a statin in combination with a cholesterol absorption inhibitor or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. Inhibition of the PCSK9 enzyme has been shown to lower LDL-C, potentially reducing cardiovascular risk. As elsewhere reviewed (45, 46), the approved PCSK9 inhibitors (evolocumab and alirocumab) are effective in reducing plasma LDL-C values by 50 to 60%, and in reducing cardiovascular event risk. Also, it has been ascertained that the use of evolocumab on top of statin is not associated with cognitive deficits, as shown by the EBBINGHAUS (Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascUlar Risk Subjects) trial (47) A meta-analysis (48) demonstrated that both alirocumab and evolocumab improved cardiovascular outcomes with good safety profiles. Consistently, the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial (49) showed that add-on therapy with evolocumab significantly lowered LDL-C levels and reduced the risk of cardiovascular events in patients with atherosclerotic cardiovascular disease. Again, the trial also showed that patients had a benefit from lowering LDL cholesterol levels below current targets. Consistently, a meta-analysis (50) found that PCSK9

inhibitors added to medium- to high-intensity statin therapy significantly reduced LDL-C in patients requiring further LDL-C reduction.

Similarly, the ODYSSEY ESCAPE (Study of Alirocumab in Patients With Heterozygous Familial Hypercholesterolemia Undergoing Low-density Lipoprotein Apheresis Therapy) trial (51), evaluating the effect of alirocumab on the rate of standard apheresis treatments in heterozygous familial hypercholesterolaemia, showed that alirocumab significantly reduced requirement for apheresis. The latter was deferred if LDL-C was at least 30% lower than the baseline (pre-apheresis) value.

A sub-analysis of the ODYSSEY COMBO II (52) found that alirocumab was more effective in reducing LDL-C levels than ezetimibe in high-risk cardiovascular patients, regardless the presence of diabetes mellitus. Similarly, the recent sub-analysis of the ODYSSEY Japan trial (53), in high-risk patients with hypercholesterolemia on stable statin therapy, found that alirocumab led to substantial and sustained LDL-C reductions over time, regardless the diabetes mellitus status at baseline.

A sub-study of the ODYSSEY-KT (54) confirmed the efficacy of alirocumab in improving lipid profile, in patients with hypercholesterolemia and high cardiovascular risk.

These results are consistent with the sub-analysis of the BIOSTAT-CHF (Biology Study to Tailored Treatment in Chronic Heart Failure) (55), a multicenter, multinational, prospective, observational study that included patients with worsening HF signs and/or symptoms. This sub-analysis found that PCSK9-LDLR axis was associated with HF outcomes, confirming its role as a risk predictor and biotarget in this population.

Accordingly, the GLAGOV trial (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) (56) showed that evolocumab not only reduced LDL-C but also led to greater plaque regression.

Finally, in patients with statin intolerance, the GAUSS-3 (Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin intolerant Subjects) trial (36) found that evolocumab led to significantly

greater reduction in LDL-C than ezetimibe, with lower occurrence of myalgia and consequent lower discontinuation rate for muscle symptoms. Thus, PCSK9 inhibitors may offer a new, safe treatment option in patients with statin intolerance (45).

However, to draw recommendations, results of the phase 3 outcome trials are needed. Now both the aforementioned FOURIER trial (49) and the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) (57) trial have been published. Both trials were positive with a relative risk reduction of about 15% - over statins in the control arm - for the majority of important endpoints.

Recommendations on the use of new lipid lowering drugs

The use of a maximally tolerated statin dose combined with non-statin lipid-lowering therapies to attain the low-density lipoprotein cholesterol targets is recommended (27). Future guidelines should point out that using a fixed combination with new lipid lowering drugs is recommended to lower the dose of statins, minimise the side effects and therefore improve adherence without reducing efficacy. To this aim, a single-pill administration is recommended.

As a first step, we advise to stratify patients, following the results of the aforementioned trials, showing that high risk patients benefit from higher reductions in LDL levels (<30 mg/dl). As such, it is also recommended to personalise the treatment according to the risk. Concordant with new US guidelines, a revaluation of correct LDL target (especially in patients at high risk profile) has always been advocated in the European guidelines (4, 5). More stringent targets for high risk patients have been recommended by the 2019 ESC/EAS Practice Guidelines for the Treatment of Dyslipidaemias. The central rationale of lipid therapy is: the higher the patients risk the lower his LDL-C goal. This means that a patient at very high risk should receive treatment that is able to attain the risk-related goal.

Two cornerstones for lowering LDL-C intensively are the establishment of LDL-C as a causal factor for atherosclerotic cardiovascular disease, e.g. by Mendelian randomization studies, and the

safety of going very low as has been demonstrated by the recent PCSK9 inhibitor trials, FOURIER , EBBINGHOUSE, and ODYSSEY OUTCOMES. Now, LDL particles are considered as a toxin, and radical reduction of a toxin is only logical.

The strategies proposed in this article are in close line with the new Guidelines. On the way to attain the LDL-C goal of 1.4 mmol/l (55 mg/dl) in very high risk patients, it is preferable to use the oral combination immediately after an event. This reduces the steps of treatment intensifications. An even lower goal is recommended for patients with recurrent events: LDL-C <1.0 mmol/L (40 mg/dl). Also from a practical view-point this is very important for the implementation of the treatment, the more steps the more barriers to reach the patient. This is also cost-effective, as is the full use of oral lipid lowering therapy if it (only slightly) reduces the need for monoclonal antibody therapy. Our proposals here therefore are not only consistent with the new guidelines but also try to facilitate their implementation.

An unsolved issue regards the difficult implementation of the new lipid lowering drugs in clinical practice mainly due to the lack of regulations in many EU countries. Strict regulatory indications (e.g. family history of hypercholesterolemia for PCSK9) also hinder their clinical use. Last but not least, in some EU countries there is no reimbursement for the new lipid lowering drugs and this is a further barrier for their implementation, in particular for PCSK9 inhibitors.

More awareness is therefore needed in medical community to overcome these barriers.

Finally, it is well-known that lifestyle modifications may improve plasma lipid profile, as acknowledged by the guidelines. In particular, the role of dietary measures in the management of dyslipidaemia is pivotal and, as such, a multidisciplinary approach also targeted at correcting nutrition is recommended.

Future research: nutraceuticals

In light of their lipid-lowering and beyond lipid-lowering effects, certain nutraceuticals have been studied as an alternative or add-on therapy to statins. In particular, red yeast rice, bergamot,

berberine, artichoke, soluble fiber, and plant sterols and stanols have been studied alone or in combination with each other, as well as with ezetimibe. Unfortunately, there are still few data to draw firm conclusions about their long-term safety and efficacy. Their effects and available data are summarised elsewhere (58).

In particular, there is randomised evidence supporting the efficacy of plant sterol ester supplements in improving lipid profile, by lowering plasma cholesterol levels, and consequently reducing cardiovascular risk (59-61). When more pharmacological data on the long-term efficacy and safety of these nutraceuticals will be collected, scientific societies will be asked to provide regulations and recommendations on their use in statin intolerant patients.

Conclusions

Non adherence should be considered as a dangerous and sometimes fatal risk factor.

It is pivotal to distinguish between statin intolerance and non adherence due to statin reluctance.

Adherence is modifiable and predictable, and as such it may be prevented and even reversed.

To this aim, fixed combinations with new lipid lowering drugs are going to change our clinical practice. In particular, combination with lower dose statin and ezetimibe in the same pill is one of the best strategies in terms of efficacy and adherence. No safety concern has been raised for the new lipid lowering medication, including cognitive impairment. However, longer follow ups are warranted.

Conflict of Interest: none declared

FIGURE 1

Main barriers to statin therapy implementation.

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Table 1. Factors leading to non-adherence to statin treatment

Causes	**Suggested strategies to improve adherence**
Complexity of treatment, polypharmacy Frequency and duration of treatment Frequent changes in treatment Cost of medication Other therapy-related factors	Single pill administration
Patient has been told about side effects Patient's misperception Lack of benefit in treatment OR immediacy of beneficial effects Lack of access to care or medication Poor relationship patient-doctor	Improve patient awareness and doctor-patient relationship Increase availability of medical support
Psychological problems, cognitive impairment	Role of caregivers
Inadequate follow up or discharge planning	Implementation of treatment plan
Statin-specific, documented side effects	Therapeutic interchange

Figure 1