SUMMARY

Cardiovascular (CV) diseases are a major burden for all the healthcare systems around the world. Public health and medical advances continue to beneficially affect CV patients health. In the last decades, many new medicinal products for hearth problems were discovered and received a marketing authorization.

Elevated low-density lipoprotein cholesterol (LDL-C) levels have been linked to major CV risk. The objective of this study was to review the medical needs in high-risk cardiovascular patients with familial hypercholesterolemia undergoing pharmacological treatment with statins and the degree of attained lipid control.

A conclusion it can be stated, that there is a significant unmet medical need for a potentially effective treatment, which can supplement the statin therapy, enabling vulnerable populations to achieve sufficient control of LDL-C, and thus provide an alternative for patients with statin intolerance or where this group of medicinal products are not clinically appropriate.

Keywords: unmet, medical, needs, high-risk, cardiovascular, patients, familial, hypercholesterolemia,

BACKGROUND

Cardiovascular diseases (CVD) are a major health problem in European countries, including Bulgaria. Each year, ischemic heart disease (IHD), a type of coronary artery disease (CAD) causes 1.8 million deaths (20% of all deaths) in Europe. In Bulgaria, diseases of the circulatory system (including ischemic heart disease and cerebrovascular disease) cause more than 71,000 deaths per year (66% of all deaths). [1] In 2014, 197 deaths due to CVD per day were reported for our country. [2] In a cross-sectional observational study, 3810 individuals from Bulgaria with a history of CVD were evaluated. The study authors used the Systematic Coronary Risk Assessment (SCORE) method and the European High-Risk Chart to calculate the total 10-year risk of a fatal cardiovascular (CV) event. The results show that approximately 11% of patients are at excessive risk and more than 13% are at very high risk (excessive risk is defined as SCORE ≥ 15%; the very high risk is defined as SCORE from 10% to 14%). [3]

Large-scale epidemiological studies have shown that elevated cholesterol in low-density lipoproteins (LDL-C) is the major reason for cardiovascular risk. Further studies indicate that levels of LDL-C are primarily regulated by cellular LDL receptors (LDLRs) and their components. The use of low-density lipoprotein cholesterol (LDL-C)-lowering medications has led to a significant reduction of cardiovascular risk in both primary and secondary prevention. [4]

Statin therapy, one of the cornerstones for the prevention and treatment of CVD, has been demonstrated to be effective in lowering LDL-C levels and in reducing the CV risk. Nevertheless, this type of medication is generally well-tolerated, compliance with statins intake remains suboptimal. One of the main reasons is limitations by multiple adverse events. [5]

REVIEW RESULTS

To minimize the risk of major CV events, it is important to reduce LDL-C levels to below 2.5 mmol/l (45 mg/dL) in patients with a high risk of major CV events or below 1.8 mmol/l (37 mg/dL) for those with very high risk. Lipid-lowering therapies may reduce the risk of CV events, but many patients continue to experience additional CV events - this is known as residual risk. [6, 7, 8] The residual risk remains despite the maximum intensity of the therapy with statins or other lipid-lowering treatments (e.g., ezetimibe, fibrates, nicotinic acid, bile acid sequestrants). [9, 10] An international study in 9 countries found that approximately 20% to 45% of patients with a high risk of CVD did not achieve sufficient reduction in LDL-C levels. [11] Of those with moderate to high risk in France, Spain, and the Netherlands, 25% to 40% did not achieve the LDL-C target values, and these patients remain at risk of major CV events.
Unmet needs for statins insufficient efficacy for lowering LDL-C

Despite the abundance of supporting data and their widespread dissemination, statins have important limitations, including limited therapeutic efficacy and risk of adverse effects. [13] Often, statin monotherapy is insufficient for lowering the risk of major CV events, especially in patients with additional risk factors, such as FH, diabetes, history of CVD, hypertension, or moderate to severe CKD. [14, 15, 16, 17] Overall, the maximum dose of the most potent statin achieves a reduction of LDL-C by 58% [18], which may not be sufficient for high-risk patients to achieve adequate control of LDL-C. In addition, the greater part of the reduction of LDL-C occurs with the initially selected statin dose [19], doubling the statin dose only leads to an additional reduction of LDL-C levels by 6% [20, 21, 22] on average and increases the risk of adverse effects. Thus, for patients with a history of MI or stroke with LDL-C > 2.6 mmol/l (47 mg/dL) who receive a moderately intensive or intensive statin dose, doubling the dose is unlikely to achieve the recommended value of LDL-C < 1.8 mmol/l (37 mg/dL). Analysis based on a meta-analysis of CTTC estimates that the potential benefits of increasing the dose of atorvastatin from 40 mg to 80 mg daily will result, in the best-case scenario, in a further reduction by 2% of the estimated prevalence of clinical CV events. Dose increases may be associated with increased adverse effects and reduced compliance. [23]

Statin intolerance leads to discontinuation of treatment or dose reduction, which places patients with increased LDL-C levels at risk of CV events. A retrospective analysis of 1 605 patients referred to cardiology clinics because of statin intolerance discovered that only 44% of the patients who have discontinued treatment with statins had achieved the therapeutic targets for LDL-C, which is significantly lower than the level observed in patients who were receiving statins intermittently (e.g. every other day or once a week) (61%, p<0.05). [24] Clinicians everywhere report that only 21% to 41% of patients with statin intolerance achieve the therapeutic targets for LDL-C, and only 26% to 43% of the patients were treated sufficiently in the opinion of their doctor. [25]

Data from the EUROASPIRE IV study show that only 22.5% of IHD patients who are intolerant to statins have levels of LDL-C < 2.5 mmol/l (45 mg/dL) during the interview, which takes place 6 months to 3 years after the indicative CV event. Of those who discontinued statin therapy, only 26.9% achieved the target levels for LDL-C. Only 3.6% of patients using low-dose statins or reducing the intensity of their statin treatment during follow-up have achieved levels of LDL-C < 2.5 mmol/l (45 mg/dL) during the interview. [26] Only 1.8% of IHD patients with statin intolerance, 1.9% of patients who have discontinued statin treatment and 9% of patients using low-dose statins or reducing the intensity of their statin treatment have achieved a reduction of LDL-C by 50% during the follow-up period. [27] Thus, there are significant unmet needs for effective alternatives of statins or additional treatment in
high-risk patients, especially those with a history of CHD that are intolerant to statins or refuse treatment with statins in order to avoid the typical adverse effects, which leads to better adherence to therapy. [28]  

Suboptimal treatment of LDL-C in familial hypercholesterolemia  
There are significant unmet needs of FH patients. High-dose statin therapy (sometimes using twice the maximum recommended statin dose) was used to reduce both LDL-C (in the range of 13% to 49%) and the CV incidence among HeFH and HoFH patients. [29, 30, 31]  

Despite the use of high-dose statins, however, less than 1 in 20 FH patients achieve the recommended target values of LDL-C. Vishwanath and Hemphill [32] calculate that statins alone and in combination with other lipid-lowering treatments can reduce LDL-C levels on average by only 25% for HoFH and 45% to 60% for HeFH [33, 34, 35, 36], which is not sufficient to achieve target LDL-C levels of <2.5 mmol/l (45 mg/dL).  

Only 7% of primary prevention patients and 24% of secondary prevention patients achieved LDL-C <2.5 mmol/l (45 mg/dL). Approximately 46% of primary prevention patients and 33% of secondary prevention patients have levels of LDL-C >4.1 mmol/l (73 mg/dL). Of HeFH patients registered after 2005 and receiving maximal lipid-lowering therapy (i.e. intensive therapy with statins plus another lipid-lowering agent), 63% are with primary prevention, and 37% are with secondary prevention. Only 17% of primary prevention patients and 23% of secondary prevention patients achieve LDL-C <2.5 mmol/l (45 mg/dL) and 25% of primary prevention patients and 27% of secondary prevention patients maintain levels of LDL-C > 4.1 mmol/l (73 mg/dL) (despite the highly intensive therapy with statins plus another lipid-lowering agent). [37]  

Fig. 2. Distribution of patients with primary and secondary prevention of heterozygous familial hypercholesterolemia depending on the level of LDL-C; LDL-C - cholesterol in low-density lipoproteins; primary prevention includes individuals with lipid-lowering therapy for prevention of initial CV events; secondary prevention includes individuals with a history of CV events with lipid-lowering therapy for prevention of recurrent CV events.
A: Patients registered after 2005 (n = 733) and classified according to LDL-C concentration and CVD risk: primary prevention (n = 640) or secondary prevention (n = 93)

B: Patients registered after 2005 and treated with maximal lipid-lowering therapy (statin S4 plus another lipid-lowering agent) (n = 181). Patients are classified according to LDL-C concentration and their CV status: primary prevention (n = 115) or secondary prevention (n = 66).

Source: Beliari et al., 2014 [37]

The CEPHEUS study (CEntralized Pan-European survey on THE Under-treatment of hypercholesterolemia) evaluates 14,478 adults receiving lipid-lowering therapy, 357 (2.6%) of them with FH. A multivariate analysis shows that FH is a negative prognostic factor to achieve the targets of LDL-C (OR = 0.71; 95% CI 0.55 - 0.92). [38] Most (56%) FH patients did not achieve levels of LDL-C < 2.5 mmol/l (45 mg/dL) according to the guidelines of the Third Joint European Task Force (JETF) for patients with FH, which is in line with current ESC guidelines. [39] In a cross-sectional study of 1,249 HeFH patients, up to 79% did not achieve their therapeutic targets while on statin treatment. Of those who did not achieve or were below target, 27% used maximum combination therapy. [40]

A cross-sectional study of adults with HeFH in the Netherlands found that only 29.5% were receiving lipid-lowering therapy with only 8.0% of them receiving highly intensive statins and 2.7% receiving a combination of highly intensive statin plus ezetimibe. Of HeFH patients with a therapeutic target <1.8 mmol/l (37 mg/dL) using lipid-lowering therapy, only 3.9% achieved this target value during the screening. Of patients with a therapeutic target <2.5 mmol/l, only 7.7% maintain this target value with lipid-lowering therapy. Since many HeFH patients begin lipid-lowering therapy with extremely high levels of LDL-C (e.g. > 4 or 5 mmol/l), [41], very few are expected to achieve LDL-C targets even with high-intensity statin therapy because of: (1) intolerance (defined as muscle pain and/or liver dysfunction) [42]; (2) not powerful enough [43]; (3) unfavorable genetic background. [44]

Modern lipid-lowering treatments do not provide sufficient LDL-C reduction in HoFH patients. The clinical diagnosis of HoFH includes an untreated level of LDL-C, which may be greater than 13 mmol/l (235 mg/dL). [45] In these cases, even a 50% reduction from baseline with a combined drug therapy would be insufficient to adequately reduce LDL-C and associated CV risk. Although it is reported that some available treatments reduce LDL-C by up to 40%, the response to these treatments is not homogeneous. [46, 47]

**Summary of unmet medical needs**

In summary, atherosclerotic CV disease remains a significant public health problem, particularly in FH patients and other high-risk groups (e.g., with a history of CVD and/or diabetes mellitus). However, despite the availability of statins and other lipid-lowering treatments, a large number of high-risk patients remain vulnerable to major CV events as they are difficult for effective treatment in clinical practice. Many patients either fail to achieve the desired levels of LDL-C with moderate- or high-dose statins or cannot tolerate statin therapy with sufficient intensity to effectively control LDL-C. Without access to safe and more effective lipid-lowering therapies that can be used in combination with statins (or individually in cases of statin intolerance), patients will remain at high risk for CVD and will continue to have excessive CV morbidity and mortality. These serious health consequences place a significant burden on the healthcare system in Bulgaria as well as on society as a whole.

**CONCLUSION**

There is a significant unmet medical need for a potentially effective treatment, which can supplement the statin therapy, enabling vulnerable populations (in particular FH) to achieve sufficient control of LDL-C, and thus provide an alternative for patients with statin intolerance or where statins are not clinically appropriate.

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