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ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Similarities and differences between European and United States guidelines for the management of dyslipidaemias

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INTRODUCTION

The first European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidaemias were published in 2011 [1]. These ESC/EAS guidelines are, when dyslipidaemias are concerned, in full accordance with more recently published Joint European societies guidelines on cardiovascular disease prevention in clinical practice (version 2012) [2]. In 2013 the American College of Cardiology (ACC) and the American Heart Association (AHA) released three documents reporting on guidelines for the prevention of atherosclerotic cardiovascular disease (ASCVD) — one document on the assessment of cardiovascular risk, one on lifestyle management to reduce cardiovascular risk, and one on "treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults", which is a corresponding document to the European ESC/EAS guidelines for the management of dyslipidaemias [3].

In this review differences and similarities between the European ESC/EAS guidelines for dyslipidaemia management and United States (US) ACC/AHA guidelines on the treatment of blood cholesterol will be commented on. This is important since in some European countries there are still physicians who tend to follow US guidelines. Also, the recent US guidelines on the treatment of blood cholesterol received mixed reviews immediately after publication and significant controversy initiating vivid discussions, not only in Europe but also even more in the US, particularly when compared with the European ESC/EAS guidelines [4]. Therefore, it is important to point out all similarities and especially all the significant differences between these two most important recent guidelines, in order to stress why is it so important for European countries to implement the European guidelines and why are they more appropriate for these countries.

There are many similarities between these two sets of guidelines, but as the differences are discussed much more, the major similarities will be briefly mentioned now and some of the differences will be later analysed in detail. The major similarities are that both of these guidelines consider that increased low-density lipoprotein-cholesterol (LDL-C) is unequivocally a causal factor for ASCVD, and both guidelines have systematically evaluated scientific evidence and have applied the grading systems, but it should be stressed that the European guidelines used the same grading system as all the other ESC guidelines [5, 6]. Both of them encourage lifestyle modification and the engagement of the patient as a partner in ASCVD prevention. Both guidelines clearly identify four

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patient groups at greatest risk of ASCVD: those with established ASCVD, those with diabetes mellitus, those with high predicted ASCVD risk based on global risk assessment, and those with familial hypercholesterolaemia (FH). However, no explicit mentioning of FH and no recommendation for these patients appears in US guidelines, although some recommendations obviously have to be applied to them [7].

The major differences are: The US guidelines consider only and exclusively the evidence originating from randomised controlled trials (RCTs) and concentrate only on LDL-C while the European guidelines consider mostly RCT evidence, but unlike the rigid US approach, they take into consideration also all available evidence and not just RCTs. They consider also the importance of all lipids and not just LDL-C and provide practical guidance across a broader range of lipid disturbances, offering much broader pragmatic clinical advise on the utility of other lipid fractions such as triglyceride-rich lipoproteins, remnants, and conditions associated with low levels of high-density lipoprotein-cholesterol (HDL-C) where non-HDL-C or apolipoprotein B are more informative, as well as lipoprotein (a), which is also considered to be a risk factor for ASCVD [8, 9]. The European guidelines also extend the scope of the definition of ASCVD to include findings from imaging and not simply a clinical presentation, thereby including patients at an earlier stage of disease. The European guidelines consider chronic kidney disease as a coronary artery disease (CAD) equivalent and therefore include these patients in a very high risk group who require lipid management with a target LDL-C of < 1.8 mmol/L (~70 mg/dL) or a 50% reduction in LDL-C whereas the US guidelines do not discuss chronic kidney disease patients at all. Another important difference is that the US guidelines focus primarily on the treatment process whereas the European guidelines focus primarily on the treatment results. European guidelines are focused not only on LDL-C as a risk factor but on individual patients, which is also different from the US guidelines.

RISK ESTIMATION

Since the treatment of dyslipidaemias should always be considered within the broader framework of ASCVD prevention, the assessment of total ASCVD risk is crucial. In European guidelines risk estimation is based upon Systemic Coronary Risk Estimation (SCORE) [10] while in the US guidelines it is based upon Framingham [11], which was used for developing a new risk pooled cohort risk calculator. Although most risk estimation systems perform rather similarly when applied to populations that are comparable to those from which the risk estimation system was derived, it has been clearly shown that the differences in populations do play a significant role [12, 13].

The SCORE system used in European guidelines estimates the 10-year risk of a first fatal ASCVD event (acute myocardial infarction, stroke, etc.). It is based upon a very large, representative (over 250,000 individuals) population from different European countries. The choice of retaining the system that estimates ASCVD mortality rather than total (fatal plus non-fatal) events in the European guidelines was deliberate. There were several reasons for this. Death is undoubtedly a hard and reproducible endpoint while a non-fatal event is variable and depends upon definitions, diagnostic criteria, and diagnostic tests, all of which may vary over time and availability in different countries. It is also clear that a high risk of ASCVD death automatically indicates a higher risk of total events. The use of ASCVD mortality allows re-calibration to allow for time-trends and for secular changes if good quality up-to-date mortality and risk factor prevalence data are available [14]. This is the case in all European countries. Unfortunately, data quality does not permit this for non-fatal events, at least in a number of European countries in which the data on ASCVD events are incomplete, but even more so for many non-European countries, excluding the US.

Since one of the advantages of the SCORE system is that it can be re-calibrated for use in different populations and adjusted for secular changes in CVD mortality and risk factor prevalence, such calibrated country-specific versions exist for a number of European countries, including Poland. Of course, risk estimation calculator based upon Framingham, as used in the US guidelines, can also be re-calibrated for countries other than the US, but the process is incomparably easier for ASCVD mortality than for total ASCVD events.

Immediately after publication there was a lot of criticism towards the recent US guidelines and also towards the new US pooled cohort risk calculator upon which these guidelines are based. Many have objected that the primary prevention threshold used in these guidelines, if applied, would result in many more patients receiving statins and in many cases with higher doses than are currently used in the US, and even more so in Europe. Particularly controversial is the utilisation of the new US risk calculator in primary care to determine which individuals will require a statin because they emphasise 10-year risk of at least 7.5% of ASCVD to identify adults 75 years of age or younger and with no established ASCVD as eligible for statin therapy for primary prevention [15]. This 10-year threshold of 7.5% corresponds to a 2.5% risk for ASCVD death over 10 years in the SCORE model used in the European guidelines and represents a much lower threshold for 10-year risk of fatal and non-fatal ASCVD. In SCORE those with a 10-year risk of fatal ASCVD of 2.5% are considered at moderate risk, and the European guidelines recommendation is that an LDL-C of < 3 mmol/L (~ 115 mg/dL) is acceptable in them. Thus, while the European guidelines allow some scope by virtue of an LDL-C target for lifestyle intervention before lipid-lowering drug therapy is introduced, patients are more likely to be treated immediately with statins following the recent US guidelines. A particular problem seems to be that according to the US guidelines practically all subjects older than 70 years, because of the impact of age on 10-year ASCVD

risk according to the US risk calculator, should be prescribed moderate- to high-intensity statin treatment.

Using the National Cardiovascular Data Registry Practice Innovation and Clinical Excellence (NCDR PINNACLE) registry data from 2008 to 2012 and a cohort of 1,174,545 patients, it has been recently established that achieving concordance with the recent US guidelines in patients treated in different US cardiovascular practices would result in significant increases in statin use, as well as significant reductions in non-statin therapies and laboratory testing [16]. The most recent analysis to date, which included 4,227 patients from the Multi-Ethnic Study of Atherosclerosis (MESA) aged 50–74 years, who were followed for 10.2 years, showed that the new US risk calculator used in the recent US guidelines, overestimated the risk of ASCVD endpoints by 86% in men and 67% in women. Overall, the US risk score overestimated risk by a net 78% [17]. The editorial that accompanied this paper stressed that such an overestimation is very important as some patients might, due to grossly overestimated risk, end up on lifelong statin therapy, and that a 7.5% risk of ASCVD events at 10 years does not automatically mandate the start of statin therapy [18]. This overestimation is particularly evident when some specific subpopulations are concerned [19]. Finally, there are data indicating that implementation of these recent US guidelines would increase the number of adults who would be eligible for statin therapy in the US by 12.8 million, with the increase seen mostly among older adults without ASCVD [20] for whom studies have not consistently demonstrated an overall beneficial effect of such a treatment on total mortality [21]. So it seems that the serious concern that the risk calculator used by the recent US guidelines will generally overpredict ASCVD risk is absolutely justified.

WHY MIGHT OVERESTIMATION OF ASCVD RISK BE SO IMPORTANT?

Possible overestimating of the risk is not only important because of drastically increased expenditures to the public health budget caused by significantly increased numbers of individuals who should therefore be treated lifelong with statins, but much more because of a higher incidence of adverse effects of statins when prescribed so extensively. These adverse effects include myopathy, which is most often defined as an increase in creatinine kinase > 10 times the upper limit of normal (ULN) with or without muscle symptoms, but also potentially life-threatening rhabdomyolysis [22]. A much more important adverse effect, particularly when life-long treatment is concerned, is diabetes mellitus [23]. Meta-analyses have associated statins with a 9–13% increase in incident type 2 diabetes, which translates to one new diagnosis of diabetes per 1,000 person-years of statin use [24–26]. This is of particular concern in individuals who are treated with high-intensity statin therapy since it has been shown that in this group for every 1,000 patient-years two additional cases of diabetes occur [27]. Recently it has been demonstrated that statin therapy increases the risk of incident type 2 diabetes even more than was supposed earlier. Based upon a recent Finnish study on 8,749 non-diabetic men aged 45–73 years in a six-year follow-up of the Metabolic Syndrome in Men (METSIM) trial, statin therapy appears to increase the risk for incident type 2 diabetes by up to 46%, even after adjustment for confounding factors, and the risk is dose-dependent for simvastatin and atorvastatin [28].

ONLY RCT OR ALL THE AVAILABLE EVIDENCE?

The US guidelines confine themselves to a single, hard source of evidence — RCTs — ignoring the much wider scientific basis of knowledge that is available. This is very different from the previous comprehensive US guidelines — the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) — NCEP ATP III guidelines [29]. Unlike this, the European guidelines are based on understanding that the knowledge concerning the causes of ASCVD and the trends in its occurrence, which are of the utmost importance for ASCVD prevention, has come from over a century of research from many diverse disciplines. So these guidelines considered not only RCTs but also other sources — clinical observations, basic science, pathological studies, genetic studies, Mendelian randomisation studies, epidemiology, meta-analyses, and systematic reviews. A good example supporting such a view is that the decline in ACVD in some countries such as Finland was associated with substantial changes in lifestyles, particularly nutritional habits, and with the consequent reduction in blood cholesterol that preceded the introduction of statins. Also, US guidelines are focused only on the drugs, more precisely only on statins, and doses that were tested in RCTs (although not always consequently), and from them only fixed-dose strategies were considered, which is quite different from real life situations.

TREATMENT TO TARGETS OR NO LIPID TARGETS AT ALL?

One of the most controversial issues concerning the recent US guidelines is their statement that "treating to target is no longer recommended". It is hard to understand why is it so because these guidelines, just like the European guidelines, as already stated, consider increased LDL-C as a causal factor for ASCVD [30]. Why do they not accept LDL-C also as a treatment target? They have abandoned treating to LDL-C targets and instead encouraged physicians to prescribe low-, moderate-, or high-intensity statin treatment depending upon the patient's baseline risk, from which four statin benefit groups were identified. They made these recommendations about specific statin intensity, specifically high-intensity in order to achieve at least a 50% LDL-C reduction, moderate-intensity to achieve a 30% to 50% LDL-C reduction, and low-intensity

in order to achieve an LDL-C reduction less than 30%, depending upon absolute risk within individuals. However, it has to be clearly stated that the percentage reduction and those numbers do not have any hard RCT evidence base, which was claimed as the sole criterion of the US guidelines since there was no RCT until today with 50% or 30% LDL-C reduction as a target.

The recent European guidelines retained their commitment to a targeted approach to LDL-C, as already accepted in previous European joint prevention guidelines [31] and defined LDL-C targets that were tailored to the level of risk, although RCTs have not, in general, examined all the different LDL-C targets systematically. Still, according to these guidelines, in patients at very high ASCVD risk the LDL-C goal is, as already mentioned, less than 1.8 mmol/L (~70 mg/dL) and/or a ≥ 50% LDL-C reduction when the target level cannot be reached, in patients at high risk the LDL-C goal is less than 2.5 mmol/L (~100 mg/dL), and in subjects at moderate risk the LDL-C target is less than 3.0 mmol/L (~115 mg/dL). Such an approach allows greater flexibility. One might, however, question it claiming that targets are not evidence based enough. Nevertheless, it has been clearly shown, for example, that extrapolating from the available data, an absolute reduction to an LDL-C level of less than 1.8 mmol/L (~70 mg/dL) or at least a 50% relative reduction in LDL-C provides the best benefit in terms of ASCVD reduction in subjects with very high risk, and therefore such a recommendation is given in the European guidelines [32]. This "at least 50%" is similar to the percentage from the US guidelines but is given only as an alternative if the 1.8 mmol/L target could not be achieved. Namely, it is clear that, for example, a decrease of only 50% LDL-C of 8.0 or 10.0 mmol/L (~ 310 or 390 mg/dL) in a patient with FH would certainly not be enough to prevent efficiently ASCVD.

The US approach contrasts the fact that many physicians, particularly during the last decade or more, have adopted the philosophy that "lower is better" but also that such an approach has been accepted by patients with established ASCVD, who have been taught for many years to strive to reach their LDL-C target. Also, it is well known that patients wish to know their target values since this improves their adherence not only to drug treatment but also to lifestyle changes. Targets are important in physicians' everyday practice, particularly considering doctor-patient communication, but they are also important to help optimise the patients' compliance and to motivate the patients. Since guidelines are not produced only for cardiologists or lipidologists but also for a much broader medical audience, primarily for general practitioners who are overwhelmed by a plethora of guidelines for different diseases, they need clear, simple messages and user-friendly recommendations, and such practitioners definitely favour target values [33]. They demand to have targets also because they help them to perform better services for their patients. Targets also help to measure the performance and enable quality control in preventive cardiology and preventive medicine in general.

Although the US guidelines do not recommend titration of LDL-C to any pre-established target values, explaining this by the fact that none of the RCTs were so designed, they do recommend deciding upon the use of statins in primary prevention using a mixed pool risk calculator, despite the fact that none of the RCTs were designed based upon this calculator data, and that this calculator has not been fully evaluated. This is another inconsistency of the US guidelines showing that the approach based solely on RCTs has not been consistently applied. The reason is most probably because such a rigid approach cannot be consistently applied at all in real world circumstances. Where consistency is concerned, it has to be mentioned also that, for example, although some important and widely prescribed doses have not been tested in RCTs, they are recommended in the US guidelines because they simply could not be ignored. The notion that physicians should consider decreasing the statin dose if LDL-C is less than 1.03 mmol/L on two occasions also does not have any RCT evidence base, despite the fact that RCTs were declared as the sole criterion for these guidelines. On the contrary, recent studies have shown that achieving much lower LDL-C levels is quite safe and could be recommended in some very high-risk patients.

WHAT TO DO WITH STATIN INTOLERANT PATIENTS?

As already mentioned, unlike the European guidelines, which recommend also the use of some non-statin lipid-lowering drugs, the US guidelines are very inflexible concerning this issue and they recommend only statins as lipid-lowering drugs. They ignore the fact that roughly 10% of individuals cannot tolerate statins long term and that statin intolerance, which is today a widely accepted phenomenon, is a reality, but this issue has not been addressed in recent US guidelines at all [34, 35]. In a recent study on 647 patients with CAD who were prescribed statins, about 20% failed to have a significant LDL-C-lowering response to treatment, and these patients experienced a significant progression of atherosclerotic plaques over a follow-up period ranging from 18 to 24 months, as measured by intravascular ultrasound. The authors of this study have suggested that physicians who adopt "the latest ACC/AHA guidelines for the management of cholesterol" may follow a strategy of "prescribe and forget" in which they fail to monitor the effect of the statin; however, "the ACC/AHA has said they still encourage monitoring to determine the extent of LDL lowering". Therefore, they suggest that for these patients step number one would be to increase their statin dose, which also supports ongoing monitoring. They have also stressed that if physicians interpret "prescribe and forget" as a principle for all statin doses, the atherosclerotic changes in these patients may still progress and they might still be at high risk of ASCVD events [36]. Since the recent US guidelines have abandoned

treating to LDL-C target values, not only the authors of this study but many other critics have objected that this might have the unintended effect of physicians prescribing statins without adequately determining whether they are achieving the desired effect of adequately lowering LDL-C. Also, although the US guidelines emphasis of high-intensity statin therapy for very high-risk patients might be justified, the reality is that clinical practice comprises significant prescribing inertia, and many physicians simply do not use high doses of statins, even in patients who are likely to have the greatest benefit [36].

Indeed, since US guidelines do not advise the use of LDL-C monitoring for measuring the therapeutic efficacy of lipid-lowering treatment and patient compliance, such a "prescribe and forget" approach might have important implications for very high-risk patients because they might be left undertreated. Although for these individuals US guidelines recommend that after the maximum intensity of statin therapy has been achieved, the addition of a non-statin drug may be considered to further lower LDL-C to acceptable levels, these guidelines do not specify exactly what might be "acceptable levels" for these patients. Also, since these guidelines are exclusively statin-oriented, they do not specify which non-statin drug might be used in combination treatment and in which doses.

"Prescribe and forget" of the "fire and forget" principle might also have another serious consequence — increased non-adherence. Already nearly a decade ago it was clearly demonstrated that adherence to statins is worse in patients treated on a "fire and forget" basis than in patients treated to a target cholesterol concentration, and that such a prescribing strategy is associated with worse cardiovascular outcomes [37]. The issue of adherence is, in everyday clinical work, by far the most important issue because 50% or more of all patients discontinue statins within one year of treatment initiation while after two years 75% of patients who were prescribed a statin for primary prevention and 40% of patients with an acute coronary syndrome were non adherent [38–40]. About 9% of all ASCVD events in Europe could be attributed to poor adherence to cardiovascular medications alone [41]. The "prescribe and forget" approach will certainly increase these unfavourable statistics.

STATIN MONOTHERAPY OR A COMBINATION WITH OTHER LIPID-LOWERING DRUGS AS WELL?

An important difference between the European and US guidelines is that the European guidelines stress the importance of combined lipid-lowering treatment if the LDL-C targets are not met or, in patients with elevated triglycerides and low HDL-C, if lifestyle interventions and monotherapy with one lipid-lowering drug are not successful. Hence, despite the fact that at the time when these guidelines were issued, i.e. almost four years ago, most patients with dyslipidaemia were treated with statins as monotherapy, it is clear that this will change in the near future [42]. Even earlier some authors hypothesised that the pattern might follow what happened with antihypertensive treatment, which was also previously based on monotherapy [43]. However, although combined lipid-lowering treatment has been a reality in everyday clinical practice around the world for many years, the US guidelines still recommend only statin monotherapy. This is even less justified today after the publication of the results of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), the first trial that has been able to demonstrate clearly an incremental clinical benefit by adding a non-statin agent to statin treatment. This trial showed on 18,144 patients that the addition of ezetimibe to 40 mg/day of simvastatin in high risk patients with acute coronary syndromes who have LDL-C ≤ 125 mg/dL (~3.2 mmol/L) caused not only significantly lower LDL-C levels but also lower primary composite endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, rehospitalisation for unstable angina, and coronary revascularisation) than statin monotherapy [44]. Therefore, if the patient is not getting the desired reduction in LDL-C, an additional lipid-lowering drug can be prescribed, as recommended by the European guidelines, in order to achieve adequate LDL-C lowering. Indeed, recently a retrospective (from 1999 to 2013) observational study including 1,000 consecutive adults treated for hyperlipidaemia and followed up for ≥ 3 years compared the applicability of current European and US guidelines and concluded that the application of the US guidelines may be associated with undertreatment of high-risk patients due to suboptimal LDL-C response to high-intensity statins in clinical practice. This study also found that adding ezetimibe to a statin substantially increased the rate of the European guidelines LDL-C target achievement together with the rate of LDL-C lowering response suggested by the US guidelines [45].

WHAT ABOUT THE RESIDUAL RISK?

The so-called "residual risk" is attributed either to the fact that a significant number of individuals retain a high ASCVD risk despite achieving the recommended LDL-C target levels by high-intensity statin treatment, or to the fact that many subjects treated with statins still have low HDL-C and elevated triglycerides [46]. Such a lipid disturbance, often called atherogenic dyslipidaemia, is typically encountered in high-risk patients with metabolic disorders like type 2 diabetes and/or obesity, which have an increasing prevalence but are largely under-diagnosed and under-treated [8, 47]. Although the contribution of low HDL-C and elevated triglycerides in increasing the ASCVD risk is still, at least to a certain degree, controversial the problem of residual risk has not been addressed at all in the US guidelines, and they totally ignore the wealth of evidence on the role of triglyceride-rich lipoproteins, remnants, conditions associated with low HDL-C, and small, dense LDL particles. Nevertheless, all of these are discussed in the European guidelines, and appropriate recommendations for possible treatment options are given therein.

WHY MIGHT UNITED STATES GUIDELINES NOT BE APPLICABLE OUTSIDE THE UNITED STATES, INCLUDING EUROPE?

Although the European guidelines were developed for European countries and are based on data obtained from European populations, they have been adopted by quite a number of non-European countries as well. However, in the past many more countries outside the US, even some European countries, have followed US guidelines. This is the reason why it should be stressed that immediately after the publication of the recent US guidelines it has been hypothesised that the mixed pooled cohorts equation used in these guidelines is unsuitable for most parts of the world outside the US as these populations were not included [33]. This particularly concerns the Asia-Pacific region. The US guidelines recommendations on high-intensity statin treatment may not be feasible in some populations since, for example, in the Chinese population a higher incidence of myopathy has been noted already at much lower statin doses [48]. This might occur as well in Japan where, based upon a pharmacokinetic study, the maximum dose of rosuvastatin was set at 20 mg/day, which is half of the maximum 40 mg/day recommended in the US and Europe [49].

It has been presumed that the reduction in the primary prevention threshold from 20% to 7.5%, according to the recent US guidelines, would result in a significantly greater number of patients treated with statins and in many patients with higher doses of statins, so that in a significant number of regions of the world this would be unaffordable but would also lead to a greater number of adverse effects due to statin therapy. Indeed recently, based on a large study population of 8,742 subjects plus data obtained from the 2008–2010 Korea National Health and Nutrition Examination Survey of 16,892 adults, the Korean authors have concluded that adopting the new US guidelines would result in the treatment of almost all Korean men and women (≥ 60 years and ≥ 70 years of age, respectively) without evidence of ASCVD [50]. Therefore, overestimating the risk and treating many more subjects with statins than is necessary would have serious financial as well as health consequences.

Although, based upon all the data discussed so far, the European guidelines seem to be a much more appropriate choice for European countries, the most important factor is their implementation. Concerning this, we have to realise that despite the fact that the majority of European physicians support the concept of preventive cardiology and treatment to the lipid target values, this still does not always reflect in their current practice, the knowledge of graduated medical students on dyslipidaemia and its treatment is not satisfactory and the general public perceptions, knowledge, and awareness of ASCVD risk factors including dyslipidaemia are insufficient [51–53]. Obviously, there are still challenges and many barriers to implement the guidelines [54]. Some of the barriers to more effective management of dyslipidaemia, particularly concerning lipid-lowering drug therapy, are also the financial constraints, especially in low- and middle-income European countries, as demonstrated by the data on differences in achieving lipid goal values in different countries [55, 56].

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