Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: http://www.tandfonline.com/loi/icmo20

The need for a new classification of cholesterol lowering therapies

Laszlo Mark, György Paragh & Kausik K. Ray

To cite this article: Laszlo Mark, György Paragh & Kausik K. Ray (2016): The need for a new classification of cholesterol lowering therapies, Current Medical Research and Opinion, DOI: 10.1080/03007995.2016.1233102

To link to this article: http://dx.doi.org/10.1080/03007995.2016.1233102

Accepted author version posted online: 07 Sep 2016.
Published online: 07 Sep 2016.

Submit your article to this journal

Article views: 10

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=icmo20

Download by: [Merck and Co Inc] **Date:** 17 September 2016, At: 07:40

Letter to the editor: The need for a new classification of cholesterol lowering therapies

Re: Cicero AFG, Morbini M, Bove M, et al. Additional therapy for cholesterol lowering in ezetimibe-treated, statin-intolerant patients in clinical practice: results from an internal audit of a university lipid clinic. Curr Med Res Opin 2016. doi: 10.1080/03007995.2016.1190326

Key words: Cholesterol, Guidelines, Lipids, Statins

Dear Editor:

Lipid lowering therapy (LLT) with statins have the strongest evidence regarding the reduction in cardiovascular (CV) events and total mortality and thus are the cornerstone of every global guideline after lifestyle. Despite this evidence there is a gap between current treatment uptake and clinical guidelines including a failure to achieve cholesterol targets in patients. We think that there are 3 main factors contributing in this difference. The first is the relative effectiveness of the available LLT, and statin intolerance and the use of alternative drugs to statins (1). The second are patient related factors and recently, considerable emphasis has been placed on improving patient compliance, in light of the extremely disappointing persistence to statin therapy. The third important factor which needs considerable attention is the view of health care professionals towards LLT and whether uncertainties in particular about the use of more potent statin regimes still persist and thus limit effective utilisation of LLT.

The Hungarian MULTI GAP study performed yearly between 2004 and 2013 on patients with known vascular disease has demonstrated a continuous decrease in LDL-cholesterol (LDL-C) level achievement over time. In the past couple of years the achieved average LDL-C level in high-risk patients was near the 2.5 mmol/l goal, but a further decrease of 0.7

JUST ACCEPTED

mmol/l would be required to reach the 1.8 mmol/l target level for very high risk patients. Among the statins used rosuvastatin and atorvastatin dominate and these potent statins are being used with increasing frequency (2,3).

More recently the annual decline in achieved LDL-C levels has plateaued. The background is unclear but includes factors such as: the reluctance of doctors to increase the statin dose; reluctance to switch to more potent statins; reluctance to initiate combination therapy when their patients do not reach target levels; or a lack of awareness of the benefits of further reductions in LDL-C in high risk groups.

The CEPHEUS study (Centralized Pan-European survey on the under-treatment of hypercholesterolaemia) has shown that failure to achieve lipid goals do not trigger further modification of LLT (4). Doubling the statin dose or changing to a more potent statin are potential options when lipid goals are not reached but the gain may be modest. For instance doubling the dose of current statin, results in a further 6% LDL-C decrease (rule of six) (5). In the Hungarian MULTI GAP study the plateau in the LDL-C decrease was observed despite the more frequent use of the most potent statins. In a retrospective database analysis using atorvastatin monotherapy less than half of patients achieved their goals (6). In a study based on rosuvastatin administration, in clinical trials rather than real world data, the 2.5 mmol/l LDL-C goal attainment was under 60%, and less than 20% of patients achieved the very high risk goal of 1.8 mmoL/l (7). In EUROASPIRE IV the LDL-C goal of 2.5 mmol/l was achieved by half of the patients, the 1.8 mmol/l by less than 30% (8).

The results of IMPROVE-IT support the “lower the better” concept and have proven that a non-statin drug which lowers LDL-C is able for significantly reducing the number of vascular events (9). These results provide us with evidence based data for the statin-ezetimibe combination.

JUST ACCEPTED

Achieving lipid goals at the first attempt

In order to improve compliance, the continuous education of patients is important. Also continuous emphasis on improving the doctors' knowledge about LLTs as data emerges is essential. Even with further education intensification of statin therapy may not offer much more incremental reduction in LDL-C thus ESC/EAS targets may not be attained as doubling statin dose only results in a further 6% reduction in LDL-C.

The 'old fashioned' LLT starts with a low dose statin and is based on titration of the dose. Since the titration often is omitted, in this type of approach initiating LLT without uptitration is believed to be one of the obvious causes of failing to achieve the target levels. Contrary to this traditional approach the ESC/EAS guidelines recommend defining the desired percentage LDL-C lowering required to achieve LDL-C goals and to start an appropriate therapy in one step (10). This could be a useful approach but requires that the physician calculate the expected percentage reduction and the best approach at the outset. This is ideal for statin naïve patients and the guidelines do not give a clear recommendation for cases already receiving LLT.

The combination of ezetimibe could be useful, to help target goal attainment and thus result in reduction of risk. Masana et al have tried to simplify the ESC/EAS guidelines by providing scenarios when statins suffice or when combination therapy is desirable based on baseline LDL-C and baseline risk (11). This approach could be ideal in statin naive patients where the desired and expected effect is predictable. The drawback of this approach, again, the lack a consideration of former LLT in patients already receiving statins.

We propose an algorithm to guide physicians when faced with patients not at goal who statin naïve or are already receiving LLT.

Table 1A presents a classification of the commonly used LLTs. Based on the expected LDL-C lowering effect the therapies are divided in 4 groups. The bile acid absorption inhibitors

JUST ACCEPTED

(resins), since it is not commonly used in the everyday LLT, are mentioned only as an option for very high intensity lipid lowering combinations as an option for patients with high starting LDL-C levels. Here we have included the fenofibrate which is primarily used in combination with statins in cases with high triglyceride and/or low HDL-cholesterol for the reduction of residual lipid risk, but its 10% LDL-C reduction is modest in effect but these mediacations are relatively inexpensive in contrast to more potent but expensive Proprotein convertase subtilisin-like kexin type 9 inhibitors (PCSK9i). The administration of nutraceuticals is acceptable in any level of risk to "help" statins' LDL-C lowering effect, and could be considered as inexpensive though less potent options before PCSK9i-s. The fenofibrate and nutraceuticals should be considered mainly in younger patients with very high LDL-C levels and in primary prevention cases. This table can be used to classify the current therapy of patients already on LLT and for choosing the appropriate therapy after the determination of the desired level for change.

- First we have to define the patient's LDL-C goal and the percent needed to reach it
- If the patient is on LLT,
    - using table 1.A classify the intensity of the treatment
    - based on the risk category using table I.B or C determine the intensity of therapy needed to reach the goal
    - using table 1.A choose the appropriate option
- for LLT naïve patients
    - based on the risk category using table 1.B or C determine the intensity of therapy needed to reach the goal
    - using table 1.A choose the appropriate option

JUST ACCEPTED

Using recommendation for a one step therapy will obviously not entirely solve the problems of achieving optimal LLT, but at least guide doctors regarding the appropriate treatment option for better LDL-C goal attainment in high and very high risk patients. The recommendation of LLTs except PCSK9i-s is for the present day practice; the use of PCSK9i-s is a very promising but expensive option currently mainly for cases with very high LDL-C, familial hypercholesterolaemia and statin intolerant very high risk patients.

Sincerely,

Laszlo Mark[a] , György Paragh[b] , Kausik K. Ray[c]

[a] Bekes County Central Hospital Pandy Kalman Section, Department of Cardiology, Gyula, Hungary

[b] Medical and Health Science Centre, University of Debrecen, 1st Department of Medicine, Debrecen, Hungary

[c] Department of Primary Care and Public Health, School of Public Health, Imperial College London, London, UK

JUST ACCEPTED

Transparency

Declaration of funding

The authors declare no conflict of interest and have received no payment in preparation of this manuscript.

Declaration of financial/other relationships

L.M.: advisory boards and/or lectures fees from Hungarian branches of Amgen, KRKA,

Richter Gedeon, Sandoz, Sanofi and MSD. G.P.: none. K.K.R.: advisory boards and/or lecture fees from Pfizer, BMS, Astra Zeneca, MSD, Kowa, Abbott, Roche, Regeneron, Sanofi, Amgen, Aegerion, Lilly, Novartis, Novo Nordisk, Boehringer Ingelheim; unrestricted research grant support from Pfizer, Regeneron, Sanofi, BMS.

References

1. Cicero AFG, Morbini M, Bove M, et al. Additional therapy for cholesterol lowering in ezetimibe-treated, statin-intolerant patients in clinical practice: results from an internal audit of a university lipid clinic. Curr Med Res Opin 2016. doi: 10.1080/03007995.2016.1190326

2. Mark L, Paragh Gy, Karadi I, Reiber I, Pados Gy. Kiss Z. How can we further improve the LDL-cholesterol target level achievement rate based on the Hungarian MULTI GAP 2011 study results and considering the new European dyslipidaemia guidelines? Arch Med Sci 2012;8:608-613.

3. Paragh Gy, Karadi I, Mark L, Reiber I, Pados Gy, Fülöp P. A MULTI GAP 2013 vizsgalat eredményei. [The results of the MULTI GAP 2013 trial]. Metabolizmus 2014;12:14-18. (In Hungarian)

4. Hermans MP, Cabezas MC, Strandberg T. et al. Centralized Pan-European survey on the under-treatment of hypercholesterolaemia (CEPHEUS): overall findings from eight countries. Curr Med Res Opin 2010; 26: 445–454.

JUST ACCEPTED

5. Illingworth DR. Management of hypercholesterolemia. Med Clin North Am 2000;84:23-42.

6. Jameson K, Zhang Q, Zhao C, Ramey DR, Tershakovec AM, Gutkin SW, Marrett E. Total and low-density lipoprotein cholesterol in high-risk patients treated with atorvastatin monotherapy in the United Kingdom: analysis of a primary-care database. Curr Med Res Opin 2014;30:655-65.

7. Mark L, Reiber I, Bajnok L, Karadi I, Paragh G. The Effect of Switching to the High-Efficient Rosuvastatin on the Success of Lipid Lowering Therapy in High Risk Patients. The CORVUS (Controlled Targets for High Vascular Risk Patients Using Effective Statins) Study. Pharm Anal Acta 2012;S10:001. doi:10.4172/2153-2435.S10-001

8. Kotseva K, Wood D, De Bacquer D, De Backer G, Rydén L, Jennings C, et al; on behalf of the EUROASPIRE Investigators. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol 2016;23:636-648. doi: 10.1177/2047487315569401. Epub 2015 Feb 16.

9. Cannon CP, Blazing MA, Giugliano RP, et al., IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387-2397.

JUST ACCEPTED

10. Reiner Z, Catapano AL, De Backer G, et al. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J 2011;32: 1769–1818.

11. Masana L, Pedro-Botet J, Civeira F. IMPROVE-IT clinical implications. Should the "high-intensity cholesterol-lowering therapy" strategy replace the "high-intensity statin therapy"? Atherosclerosis 2015;240:161-162.

JUST ACCEPTED

Table 1.

A. Classification of the commonly used cholesterol lowering therapies (after Masana)

LICLT (Low intensity cholesterol lowering therapy) LDL-C lowering < 30%
Simvastatin10 mg
Pravastatin 10-20 mg
Pitavastatin 1 mg
Ezetimibe

MICLT (Mild intensity cholesterol lowering therapy) LDL-C lowering 30-49%
Atorvastatin 10-20 mg
Rosuvastatin 5-10 mg
Simvastatin 20-40 mg
Fluvastatin XL 80 mg
Pitavastatin 2-4 mg
Simvastatin 10 mg + ezetimibe
Pravastatin 20 mg + ezetimibe
Pitavastatin 1 mg + ezetimibe

HICLT (High intensity cholesterol lowering therapy) LDL-C lowering 50-60%
Atorvastatin 40-80 mg
Rosuvastatin 20-40 mg
Simvastatin 20-40 mg + ezetimibe
Fluvastatin XL 80 mg + ezetimibe
Pitavastatin 2-4 mg + ezetimibe
Pravastatin 40 mg + ezetimibe
Atorvastatin 10-20 mg + ezetimibe
Rosuvastatin 5-10 mg + ezetimibe

VHICLT (Very high intensity cholesterol lowering therapy) LDL-C lowering > 60%
Atorvastatin 40-80 mg + ezetimibe
Rosuvastatin 20-40 mg+ ezetimibe
Any HICLT + bile acid absorption inhibitor
Any HICLT or VHICT + fenofibrate and/or nutraceuticals

JUST ACCEPTED

B. Recommendation for lipid lowering therapy in very high risk patients to achieve the 1.8 LDL-cholesterol goal

	Recommended LDL-C lowering group for patients			
Starting LDL-C level	statin naive	on low intensity cholesterol lowering therapy	on middle intensity cholesterol lowering therapy	on high intensity cholesterol lowering th
1.80-2.49	MICLT	HICLT	VHICLT	VHICLT
2.50-3.59	HICLT	VHICLT	VHICLT+ PCSK9i	VHICLT+ PCSK9i
3.59-4.99	VHICLT	VHICLT+ PCSK9i	VHICLT+ PCSK9i	VHICLT+ PCSK9i
5.00-	VHICLT+ PCSK9i	VHICLT+ PCSK9i	VHICLT+ PCSK9i	VHICLT+ PCSK9i

C. Recommendation for lipid lowering therapy in very high risk patients to achieve the 2.5 LDL-cholesterol goal

	Recommended LDL-C lowering group for patients			
Starting LDL-C level	statin naive	on low intensity cholesterol lowering therapy	on middle intensity cholesterol lowering therapy	on high intensity cholesterol lowering th
2.50-3.55	LICLT	MICLT	HICLT	VHICLT
3.60-4.99	MICLT	HICLT	VHICLT	VHICLT+ PCSK9i
5.00-5.99	HICLT	VHICLT	VHICLT+ PCSK9i	
6.0	VHICLT	VHICLT+ PCSK9i		

JUST ACCEPTED