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Update About the Management of Low-Density Lipoprotein Cholesterol and Hypertriglyceridemia in Lower Extremity Peripheral Artery Disease Patients: Consensus of the French Society of Vascular Medicine and the French Society for Vascular and Endovascular Surgery

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Background: A French intersociety consensus on behalf the Société Française de Médecine Vasculaire and the Société de Chirurgie Vasculaire et Endovasculaire was proposed in 2021 for the management of patients with lower extremity peripheral artery disease (LEAD). Recent studies have been published and an update of this consensus about the management of low-density lipoprotein cholesterol (LDLc) and hypertriglyceridemia was required.

Methods: A steering committee of 12 vascular physicians and surgeons defined questions of interest about LDLc and hypertriglyceridemia management. A French expert panel voted the proposals. Consensus was considered to have been achieved if more than 80% of the responses corresponded to either ''Agreement'' or ''Disagreement''.

Results: Among the 56 experts who were asked to participate, 46 (82%) accepted. After the first round of the Delphi procedure, the 4 proposals reached consensus. The following suggestions and recommendations were approved: 1. For LEAD patients treated by the highest tolerated statin dose ± ezetimibe and who have an LDLc $\geq$0.70 g/L, we recommend adding a proprotein convertase subtilisin/kexin type 9 inhibitor. 2. For LEAD patients treated by statin and who have elevated triglyceride level between $\geq$150 mg/dL and $\leq$500 mg/dL, we suggest adding Icosapent Ethyl. 3. Before adding Icosapent Ethyl in LEAD patients treated with statin, we suggest looking for symptoms that may suggest atrial fibrillation. 4. For LEAD patients treated by Icosapent Ethyl and who have symptoms that suggest atrial fibrillation, we recommend performing an electrocardiogram.

Conclusions: This update will help clinicians to improve LEAD patient management.

INTRODUCTION

The Société Française de Médecine Vasculaire (SFMV) and the Société de Chirurgie Vasculaire et Endovasculaire (SCVE) have recently proposed a consensus about the management of lower extremity peripheral artery disease (LEAD).[1] The objective of this consensus was to analyze the disparities between the different international guidelines (*American Heart Association* (AHA),[2] the *European Society of Cardiology/European Society for Vascular Surgery* (ESC/ESVS),[3] the *European Society for Vascular Medicine* (ESVM),[4] and the *Society for Vascular Surgery* (SVS),[5] as well as certain issues not covered, and develop proposals with regard to these points. In this aim, a Delphi method was performed and results were published in 2021 in the present journal.[1]

The management of dyslipidaemia in the context of LEAD was discussed in the consensus but due to the absence of availability of some treatments in France some proposals did not achieve the consensus that was set to 80% of the responses corresponding to either ''Agreement'' or ''Disagreement''.

Two major therapeutics (proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor; icosapent ethyl, a stable and highly purified ethyl ester of the omega-3 fatty acid, eicosapentaenoic acid were not available for the prescription by vascular physicians or reimburse or data on LEAD patients were not available at the time of the consensus.[6,7] In the *Journal Officiel* (JORF n°0186 du 30 juillet 2020, French law), evolocumab, a PCSK9 inhibitor, was validated by the French Health Ministry in the following case[8–10]: ''*In combination with an optimized lipid-lowering treatment in adult patients with very high cardiovascular (CV) risk, with primary hypercholesterolemia or mixed dyslipidemia, presenting with atherosclerotic CV disease defined by a history of myocardial infarction (MI), or cerebrovascular accident (CVA) nonhemorrhagic and/or lower limb symptomatic peripheral artery disease (PAD) (secondary prevention), and uncontrolled Low-Density Lipoprotein cholesterol (LDLc) $\geq$0.70 g/L despite optimized treatment including at least one maximum tolerated dose statin.*'' Initially, only cardiologists, endocrinologists or internal medicine specialists were authorized to prescribe PCSK9 inhibitor. Since March 18th, 2021, ANSM (Agence Nationale de Sécurité du Médicament) has permitted vascular physicians to prescribe PCSK9 inhibitor (evolocumab (REPATHA®) and alirocumab (PRALUENT®).[11] Alirocumab can be prescribed too but only in the following case[12]: « *In combination with an optimized lipid-lowering treatment in adult patients with atherosclerotic CV disease established by a history of recent ACS (Acute Coronary Syndrome, secondary prevention) and with uncontrolled LDLc ($\geq$0.70 g/L) despite optimized lipid-lowering agent treatment comprising at least one statin at the maximum tolerated dose*''.

Icosapent ethyl (VAZKEPA®) was authorized by the HAS (Haute Autorité de Santé) on December 15th, 2021 in the following condition[13–15]: ''*Opinion in favor of reimbursement only in adult patients on treatment with a statin at the maximum tolerated dose, with*

very high CV risk due to established CV disease (secondary prevention) and presenting with moderately high hypertriglyceridemia (≥150 and <500 mg/dL)''. Icosapent ethyl should obtain reimbursement soon in France.

Therefore, the aim of this update is to re-evaluate the proposals about the management of LDLc and hypertriglyceridemia in the context of LEAD using the Delphi method.[16]

METHODS

Design

A Delphi method that is an effective consensus technique was used to assess expert opinions about the management of LDLc and hypertriglyceridemia in patients with LEAD. In brief, a steering committee determine the questions of interest in a specific field and ask experts in the field to vote on different proposals based on the literature summarized by the steering committee. It should be emphasized that no member of the steering committee was involved in grading these proposals. This step was entrusted to the panel of experts, who received the text developed by the steering committee as well as a link enabling on-line responses and a vote on each of the proposals. The experts were asked to grade 2 proposals that initially did not obtain consensus. For each proposal they were asked if they (1) strongly agreed, (2) tended to agree, (3) had no opinion, (4) tended to disagree, or (5) totally disagreed. A space was provided for comments on each proposal, constituting a source of possible explanations for the respondent's attribution of a particular grade.

Steering Committee

The steering committee, which wrote the previous consensus about LEAD management, comprising 12 vascular physicians (GM, GB, ABR, JC, PL, CLH, GP, APM, MS) and surgeons (NC, YG, JP) with expertise in LEAD, wrote new proposals about the management of LDLc and hypertriglyceridemia in patients with LEAD(1).

Expert panel

A French multiregional panel comprising 56 experts, vascular medicine physicians and vascular surgeons, were asked to answer to the Delphi. After their acceptation, the experts had to grade the proposals by vote according to the Delphi method.

Achievement of Consensus

Consensus was considered to have been achieved if more than 80% of the responses corresponded to either ''Agreement'' (grades 1 and 2) or ''Disagreement'' (grades 4 and 5). It is important to note that the percentage consensus was calculated on the basis of all the responses submitted by the experts, including those stating ''No opinion''. If consensus was not achieved, a second vote was organized after clarification of the text and modification of the proposals if these were considered to be unclear. The votes were recorded progressively and the text was finalized at a plenary consensus meeting of experts by attribution of 1 the following 4 grades to each proposal:

- Grade 1+: strong positive recommendation: ''we recommend doing or prescribing''
- Grade 2+: positive suggestion, ''we suggest doing or prescribing''
- Grade 1−: strong negative recommendation, ''we recommend not doing or prescribing''
- Grade 2−: negative suggestion, ''we suggest not doing or prescribing''

Proposals about the management of LDLc and hypertriglyceridemia that were evaluated by the Delphi:

In the initial consensus (2021), the following proposals did not obtain consensus and the supposed reasons are presented in italic[1]:

1. For patients at very high CV risk, insufficiently stabilized by combined treatment with a statin and ezetimibe, we suggest adding a PCSK9 inhibitor. *This proposal obtained a consensus agreement of 78%, 9 experts (22%) expressing no opinion. PCSK9 inhibitors were only recently granted reimbursement status for this indication in France (in July/August 2020) and that might have influenced the responses of the experts. This proposal was prompted by the results of the randomised FOURIER trial which demonstrated a substantial benefit of additionally treating patients with a PCSK9 inhibitor.*[10]
2. For patients presenting hypertriglyceridaemia, we suggest using icosapent ethyl. *This proposal obtained a consensus agreement of 51%, 18 experts (44%) expressing no opinion. The results of the REDUction of Cardiovascular Events with icosapent ethyl-Intervention Trial (REDUCE-IT) trial were published during the second round of proposal grading.*[14] *This trial was conducted in patients with CV disease or diabetes but not specifically in those with LEAD.*

We decided to resubmit these 2 proposals with slight modifications to the panels of experts and to ask them about 2 new proposals:

1. For LEAD patients treated by the highest tolerated statin dose ± ezetimibe and who have an LDLc ≥0.70 g/L, we recommend adding a PCSK9 inhibitor.
2. For LEAD patients treated by statin and who have elevated triglyceride (TG) level between ≥150 mg/dL and ≤500 mg/dL, we suggest adding Icosapent Ethyl.
3. Before adding Icosapent Ethyl in LEAD patients treated with statin, we suggest looking for symptoms that may suggest atrial fibrillation (AF).
4. For LEAD patients treated by Icosapent Ethyl and who have symptoms that suggest AF, we recommend performing an electrocardiogram.

RESULTS

Among the 56 experts who were asked to participate, 46 (82%) accepted. After the first round of the Delphi procedure, the 4 proposals reached consensus. Thus, no second round was needed. Table I presented the results of the Delphi procedure according to each proposal. The proposal ''1. For LEAD patients treated by the highest tolerated statin dose ± ezetimibe and who have an LDLc ≥0.70 g/L, we recommend adding a PCSK9 inhibitor.'' obtained a consensus of 93%. The proposal ''2. For LEAD patients treated by statin and who have elevated TG level between ≥150 mg/dL and ≤500 mg/dL, we suggest adding Icosapent Ethyl.'' obtained a consensus of 87% as well as the proposals 3 and 4.

DISCUSSION

The current Delphi method validated 4 proposals for the management of LDLc and hypertriglyceridemia in patients with LEAD: one proposal about the use of PCSK9 inhibitors and 3 about the use of Icosapent Ethyl. These new proposals complete other proposals that were previously validated in the original consensus (Fig. 1).

PSCK9 inhibitors

The guidelines issued by the AHA, the ESC-ESVS and the ESVM concur in recommending the use of a statin for all patients with LEAD (grade 1A), even those with asymptomatic disease, the different statins available varying in their intensity (Table II).[17] The ESVM and the SVS set a target threshold for LDLc of <0.70 g/L (grade IC) or a decrease in LDLc >50% if the baseline level is between 0.70 g/L and 1.35 g/L.[4,5] In the event of intolerance or difficulty in achieving the target concentration of LDLc, the ESVM proposes the concomitant use of ezetimibe (grade IIa B).[4] Based on the results of the FOURIER trial, the ESVM proposes the further addition of a PCSK9 inhibitor (evolocumab) if treatment with a statin at the maximum tolerated dose plus ezetimibe proves ineffective.[4]

The latest guidelines of the ESC and the European Atherosclerosis Society (EAS) concerning dyslipidaemias specify the indications for prescription of a PCSK9 inhibitor in patients with LEAD(18). For these patients a lipid-lowering treatment comprising a statin at the maximum tolerated dose, ezetimibe and if necessary a PCSK9 inhibitor (Class I, level A), is recommended to reduce the risk of an adverse event associated with the CV disease.[18]

The ESC guidelines concerning dyslipidaemias establish 4 classes of CV risk.[18] Besides the SCORE classification (http://www.heartscore.org), which evaluates the 10-year risk of fatal CV disease, the ESC also takes into account the duration of diabetes (type 1 or type 2), target organ damage, family history of hypercholesterolemia, the presence of moderate or severe renal insufficiency, CV history in general, including the presence of atherosclerotic plaques in the carotid and/or femoral arteries and the coronary artery calcium (CAC) score established by computed tomography scan. The presence of atherosclerotic plaques in the carotid and/or femoral arteries increases the patient's level of CV risk.[18] A patient with LEAD or >50% carotid artery stenosis is considered to be at very high CV risk. Initial treatment comprises respect of a healthy lifestyle and dietary regime, comprising no exposure to tobacco in any form, a diet low in saturated fats and rich in whole-grain cereals, fruits, vegetables and fish, regular moderate physical activity almost every day (3.5−7 h per week or 30−60 min/day), weight control (Body Mass Index [BMI] 20−25 kg/m^2, abdominal circumference <94 cm for men and <80 cm for women) and maintenance of systolic blood pressure at <140 mm Hg. In these patients at very high CV risk, the ESC recommends for primary or secondary prophylaxis, a reduction in LDLc level of at least 50% relative to baseline and an absolute LDLc level of <0.55 g/L. Medical treatment constitutes in the first instance a statin at the maximum tolerated dose, possibly combined with ezetimibe and if necessary, based on the results of the FOURIER trial, a PCSK9 inhibitor.[10]

Table I. Results (number of experts) of the Delphi for each proposal

Proposals	1. For LEAD patients treated by the highest tolerated statin dose ± ezetimibe and who have an LDLc ≥0.70 g/L, we recommend adding a PCSK9 inhibitor	2. For LEAD patients treated by statin and who have elevated TG level between ≥150 mg/dL and ≤500 mg/dL, we suggest adding icosapent Ethyl.	3. Before adding icosapent Ethyl in LEAD patients treated with statin, we suggest looking for symptoms that may suggest AF.	4. For LEAD patients treated by icosapent Ethyl and who have symptoms that suggest AF, we recommend performing an electrocardiogram.
Strongly agreed	31	14	22	29
Tended to agree	12	26	18	11
Had no opinion	1	4	5	6
Tended to disagree	2	1	1	0
Totally disagreed	0	1	0	0

Suggestions and recommendations validated in the previous consensus (2021).

1. **For LEAD-patients, we recommend optimization of lifestyle and dietary habits in terms of body weight, smoking, diet, physical exercise, etc. (Grade 1+).**
2. **For LEAD-patients, we recommend maintaining LDLc below 0.55 g/L or at least reducing the LDLc level by half compared to its baseline value (Grade 1+).**
3. **For LEAD-patients, we recommend treatment with a statin in the first instance, adjusting the dose according to efficacy and tolerability (Grade 1+).**
4. **For LEAD-patients, we recommend the addition of ezetimibe to statin treatment if necessary (Grade 1+).**
5. **We suggest NOT TO use fibrates to reduce morbidity and mortality in LEAD-patients (Grade 2-).**

New suggestions and recommendations based on the Delphi.

1. **For LEAD-patients treated by the highest tolerated statin dose +/- ezetimibe and who have a LDL cholesterol ≥ 0.70g/L, we recommend adding a PCSK9 inhibitor. (Grade 1+)**
2. **For LEAD-patients treated by statin and who have elevated triglyceride level between ≥ 150mg/dL and ≤ 500mg/dL, we suggest adding Icosapent Ethyl. (Grade 2+)**
3. **Before adding Icosapent Ethyl in LEAD-patients treated with statin, we suggest looking for symptoms that may suggest AF. (Grade 2+)**
4. **For LEAD-patients treated by Icosapent Ethyl and who have symptoms that suggest AF, we recommend performing an electrocardiogram. (Grade 2+)**

Fig. 1. Summary of the consensus for the management of LDLc and hypertriglyceridemia in patients with LEAD.

In the FOURIER trial, 3,642 patients with LEAD (including 2,518 presenting intermittent claudication and an ankle-brachial index <0.85, 2,067 with a history of revascularization and 126 with a history of amputation), having a LDLc level >0.70 g/L and being treated with a statin, were

Table II. Intensities of currently available statins[17]

	Low intensity	Moderate intensity	High intensity
Decrease in LDLc[a]	<30%	30−49%	≥50%
Statins	Simvastatin 10 mg	Atorvastatin 10 mg (20 mg)	Atorvastatin (40 mg[c]) 80 mg
		Rosuvastatin (5 mg) 10 mg	Rosuvastatin 20 mg (40 mg)
		Simvastatin 20−40 mg[b]	
	Pravastatin 10−20 mg	Pravastatin 40 mg (80 mg)	…
	Lovastatin 20 mg	Lovastatin 40 mg (80 mg)	
	Fluvastatin 20−40 mg	Fluvastatin XL 80 mg	
		Fluvastatin 40 mg BID	
		Pitavastatin 1−4 mg	

[a]Expected decrease in LDLc at the dose indicated in each intensity category.
[b]Although simvastatin 80 mg was evaluated in randomized controlled trials, initiation of simvastatin treatment at 80 mg or titration to 80 mg is not recommended by the Food and Drug Administration owing to the increased risk of myopathy, including rhabdomyolysis.
[c]Robust evidence from 1 randomized trial only: in the IDEAL study, the dose of atorvastatin was decreased if 80 mg was not tolerated.

randomized to receive either evolocumab (140 mg every 15 days or 420 mg per month) or a placebo and followed up for a median of 26 months.[10] Half the patients (49.8%) suffered from coronary artery disease and 15% had previously experienced an ischemic stroke. Compared to a placebo, evolocumab decreased the level of cholesterol (LDLc) by 59% (95% confidence interval (CI) 57−61) achieving a median LDLc level of 0.30 g/L. Evolocumab also reduced the incidence of major adverse CV events (including CV death, myocardial infarct, stroke, coronary revascularization and unstable angina) (hazard ratio (HR) 0.79, 95% CI 0.66−0.94, $P = 0.0098$). In the FOURIER trial population as a whole, the absolute risk reduction with evolocumab was greater in patients with LEAD (3.5% (95% CI 0.8%−6.2%)) than in those without LEAD (1.6% (95% CI 0.7%−2.5%)) (133). Overall, the incidence of MALE (Major Adverse Limb Events) was reduced by 42% (HR 0.58, 95% CI 0.38−0.88). Of interest, no significant adverse effect was reported with evolocumab.

Icosapent ethyl

The fibrates granted a marketing authorization in France (AMM) so far have not proved their efficacy in reducing morbidity and mortality.[19,20] Regarding omega-3 fatty acid medicines containing a combination of an ethyl ester of eicosapentaenoic acid and docosahexaenoic acid, EMA (EMA/19056/2019) confirmed that these medications are not effective in preventing CV events. However, the REDUCE-IT trial which included 8,179 patients (71% with established CV disease) demonstrated the benefit of Icosapent Ethyl in reducing morbidity and mortality (HR 0.75; 95% CI 0.68−0.83; $P < 0.001$) in patients treated by statins with moderately elevated TG ≥135 mg/dL and <500 mg/dL).[14] At the time of the first consensus, LEAD patients were not specifically investigated. On November 13th, 2021, results of the REDUCE-IT PAD trial were presented at the AHA congress. In this study, the authors assessed whether Icosapent Ethyl benefit extends to patients included with LEAD defined as patients with ankle-brachial index <0.90 with symptoms of intermittent claudication or patients with a history of aorto-iliac or peripheral artery intervention.[15] These LEAD patients were high risk patients treated with statins and who had fasting TG levels between ≥150 mg/dL and ≤500 mg/dL. In this study, primary endpoint was CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. Secondary endpoint was CV death, myocardial infarction, or stroke. Total (first plus recurrent) events (CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina) were also studied. Among the 5,785 (70.7%) REDUCE-IT patients enrolled with established CV disease, 688 had LEAD. In the subanalysis of this study, the authors compared Icosapent Ethyl (2g) twice a day to placebo. The primary endpoint event rate (CV death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina) with LEAD was 26.2% with Icosapent ethyl versus 32.8% with placebo (HR 0.78; 95% CI 0.59, 1.03; $P = 0.08$) and total events were 112.8 per 1,000 patient-years with icosapent ethyl versus 162.3 with placebo (RR 0.68; 95% CI 0.48, 0.95; $P = 0.03$). Note that only a trend was found for the primary endpoint mainly due to a lack of statistical power in this subanalysis of LEAD patients whereas the results were highly significant in the whole population (i.e., patients with CV disease).

Primary endpoint absolute risk reductions and numbers needed to treat for the primary endpoint suggest benefit for patients with LEAD (absolute risk reduction 6.6%; numbers needed to treat 15). The authors stated that safety did not differ substantially by PAD history and was generally consistent with the overall REDUCE-IT study.[14] An increased risk of AF was found in the Icosapent Ethyl group versus the placebo group (5.8% vs 4.5%) without any increase of ischemic stroke. This increase was more frequent in patients with a history of previous AF.

CONCLUSION

These new practical guidelines about the use of PCSK9 inhibitors and Icosapent Ethyl will help to improve the management of LEAD Patients. Combination of these therapeutics with antithrombotic therapy might improve patient outcomes.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.avsg.2023.08.023.

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