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Global Spotlights

The International Lipid Expert Panel (ILEP)—the role of 'optimal' collaboration in the effective diagnosis and treatment of lipid disorders

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Statins have been commonly available for almost 30 years. Combination therapy with ezetimibe, fenofibrate, and PCSK9 inhibitors has been possible for the last 4–15 years. Furthermore, recent advances have added inclisiran and bempedoic acid to the lipid-lowering formulary. Nevertheless, only one-third of patients achieve their target levels of low-density lipoprotein cholesterol (LDL-C), based on the European guidelines 2019.[1,2] Furthermore, only 18% of patients reach the goal of <55 mg/dL (1.4 mmol/L) for those at very high risk of cardiovascular disease (CVD). When we look specifically at the region I represent—Central Eastern European (CEE) countries, the challenge is even greater, as only one quarter of patients achieve the goal, and only 13% reach the lowest LDL-C goal for the highest risk population.[1,2] When we add that compliance and adherence with therapy in these countries (also including Southern Europe, Russia, and Asian countries) is very low, and the healthcare systems are very diverse—with substantial differences in the availability of lipid-lowering therapies, including statins (not all statins are available, and sometimes very strict criteria apply to indications for which they can be supplied), ezetimibe (which is often unavailable or prescribed only by specialists) and very restricted reimbursement for PCSK9 inhibitors, this picture looks extremely worrying.[1,2] Finally, in many of those countries, there are no registries for lipids [e.g. for familial hypercholesterolaemia (FH)], nor for acute coronary syndrome, no coordinated care for the highest risk patients, no guidance, no standardized discharge letters, and no suitable monitoring of these patients.[1,2] For last 20–30 years, most of the experts from these countries have not been included in international working groups, advisory boards, steering committees, and guideline committees and have not been invited as lecturers for international congresses.

Obviously, there are many reasons, why we have not been successful, and the fault was partly due to the fact that we did not make attempts to publish in the best scientific journals, we did not send sufficient numbers of high-quality abstracts to conferences, and we did not apply for EU (and other) grants (especially as coordinators). When I was Undersecretary of State at the Polish Ministry of Science and Higher Education (2010–2012), we comprehensively discussed the issue of underrepresentation of CEE and Eastern Partnership countries in EU grants and committees and founded some dedicated calls for these investigators. However, we should also remember that success will only occur when both sides work together and try hard, as willingness is not enough. High-quality grant applications are necessary and lead to the publishing of high-quality, novel results, which can be effectively implemented in practice. The experience and learning gained in the process facilitates successful applications for subsequent (and bigger) grants.

That is why, to overcome at least some of the above-mentioned scientific and clinical gaps and unmet clinical needs, I first founded *the Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group* in 2012, and since that time, a group of >100 experts have published 69 meta-analyses. Second, in 2015, I assembled a group of almost 90 experts representing over 50 national societies and research groups—*the International Lipid Expert Panel* (*ILEP*; https://ilep.eu). From the outset, we aimed to be a panel of experts, people working together on concrete activities, without any ambitions to be a society. What is more, I still strongly believe that ILEP might be a wonderful platform to work together and to perform joint initiatives for all the societies focused on preventive cardiology, atherosclerosis and lipidology. Only by working together, can we achieve the results we desire, only together can we get the best grants, and finally change the picture of diagnostic and therapeutic ineffectiveness—and consequently address the high morbidity and mortality, which results from lipid disorders and atherosclerotic cardiovascular disease. Since that time, we have been able to prepare and have endorsed almost 30 analyses, expert opinions and position papers on the most demanding issues, not only on those that were missed in the existing guidelines, but especially to give a clear

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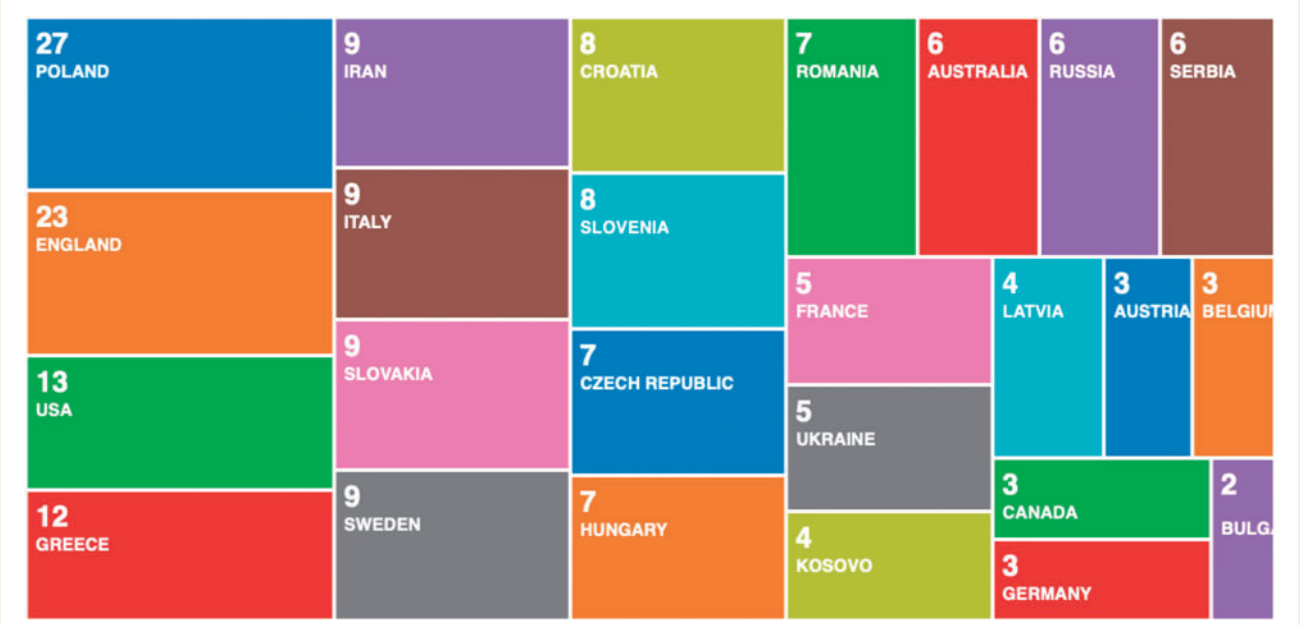

Figure 1 Results analysis of the International Lipid Expert Panel papers (n = 30) published in and indexed in Web of Science (Clarivate) by countries/regions.

Figure 2 Results analysis of the International Lipid Expert Panel papers (*n* = 30) published in and indexed in Web of Science (Clarivate) by authors.

clinical message on the management of patients (see *Figures 1–3*). In 2015, we began with an important position paper on the definition of statin intolerance, and the risk factors for this condition.[3] Next, we decided to focus on the very debateable issue of using nutraceuticals for CVD patients, knowing that natural products have very limited data on efficacy and safety (nutrivigilance) and that in most of the countries they are overused, sometimes replacing indicated pharmacotherapy. That is why in 2017 we published the first recommendations on the applications of nutraceuticals in patients with lipid disorders,[4] and in 2018, a further position paper on the role of nutraceuticals in statin

Figure 3 Results analysis of the International Lipid Expert Panel papers ($n = 30$) published in and indexed in Web of Science (Clarivate) by source titles.

intolerant patients.[5] In subsequent papers, we also discussed their applications in patients with metabolic syndrome and as a therapeutic support in patients with heart failure.[6] Recently, we have been working on the recommendations on their role in inflammation. In the meantime (in 2018), we focused on so-called *nocebo effect*, the phenomenon, which might be responsible for the statin discontinuation in over 40% of patients.[7] We proposed to change the name of this phenomenon to *drucebo effect*, as the term 'nocebo effect' is incorrect applied in this context from the pharmacodynamic point of view.[7] We are currently working on the first recommendations on how to manage with the patients with drucebo effect. Our next few papers were focused on diet, we published the largest analyses on the low carbohydrate diet and its relationship with the long-term outcomes, on the role of dairy products as well as dietary fats on all-cause and cause-specific mortality and published the first guidelines on the impact of type of dietary protein in modifying cardiometabolic risk factors.[8] It is also worth emphasizing that in 2020 we published the first recommendations on statin therapy in athletes and patients performing regular intense exercise, as for many years there has been inconsistent approach on how to manage such patients. This is of increasing importance, as regular exercise is indicated in patients with CVD and after myocardial infarction, however, intensive exertion might increase the risk of statin-related myalgia and myopathy.[9] At the beginning of the coronavirus pandemic, we noticed that there were substantial difficulties relating to the diagnosis, monitoring, and therapy of severe hypercholesterolemic patients, including those with FH. In collaboration with FH Europe—The European FH Patient Network, we published recommendations on how to manage with such patients—not only for physicians, but also for patients, patients' organizations, and healthcare providers.[10] Finally, we recently published the first recommendations on the group of patients that might benefit the most from immediate (during diagnosis and/or hospitalization) combination lipid-lowering therapy (double and triple), in which we also presented a new definition of the extremely high-risk patients, based on current evidence-based medicine.[1]

In addition to the above-mentioned recommendations, ILEP is involved in educational activities, and during the pandemic, we organized numerous webinars for participants from 85 countries. At the same time, we have been working to further support the attempts of the experts of the countries especially those from CEE, Southern Europe, and Asia to increase their opportunities to use and have reimbursed both old (statins and ezetimibe) and new innovative drugs (PCSK9 inhibitors, siRNA-related therapy—inclisiran and bempedoic acid).

Finally, I would like to strongly emphasize, that in the ILEP everyone can initiate a new idea, everyone is equal (I only Co-ordinate all the efforts), and we are a group of friends, for whom collaboration and prevention are the key words. Thus, feel invited to work with us! Only together, can we achieve success. When we work together, nothing is impossible.

References

1. Banach M, Penson PE, Vrablik M, Bunc M, Dyrbus K, Fedacko J, Gaita D, Gierlotka M, Jarai Z, Magda SL, Margetic E, Margoczy R, Durak-Nalbantic A, Ostadal P, Pella D, Trbusic M, Udroiu CA, Vlachopoulos C, Vulic D, Fras Z, Dudek D, Reiner Ž; ACS EuroPath Central & South European Countries Project. Optimal use of lipid-lowering therapy after acute coronary syndromes: a Position Paper endorsed by the International Lipid Expert Panel (ILEP). *Pharmacol Res* 2021;**166**:105499.
2. Cybulska B, Kłosiewicz-Latoszek L, Penson PE, Nabavi SM, Lavie CJ. Banach M; International Lipid Expert Panel (ILEP). How much should LDL cholesterol be lowered in secondary prevention? Clinical efficacy and safety in the era of PCSK9 inhibitors. *Prog Cardiovasc Dis* 2020; doi: 10.1016/j.pcad.2020.12.008.
3. Banach M, Rizzo M, Toth PP, Farnier M, Davidson MH, Al-Rasadi K, Aronow WS, Athyros V, Djuric DM, Ezhov MV, Greenfield RS, Hovingh GK, Kostner K, Serban C, Lighezan D, Fras Z, Moriarty PM, Muntner P, Goudev A, Ceska R, Nicholls SJ, Broncel M, Nikolic D, Pella D, Puri R, Rysz J, Wong ND, Bajnok L, Jones SR, Ray KK, Mikhailidis DP. Statin intolerance—an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch Med Sci* 2015;**11**:1–23.
4. Cicero AFG, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, Fras Z, Katsiki N, Langlois M, Latkovskis G, Panagiotakos DB, Paragh G, Mikhailidis DP, Mitchenko O, Paulweber B, Pella D, Pitsavos C, Reiner Ž, Ray KK, Rizzo M, Sahebkar A, Serban MC, Sperling LS, Toth PP, Vinereanu D, Vrablík M, Wong ND,

Banach M. Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. *Nutr Rev* 2017;**75**:731–767.
5. Banach M, Patti AM, Giglio RV, Cicero AFG, Atanasov AG, Bajraktari G, Bruckert E, Descamps O, Djuric DM, Ezhov M, Fras Z, von Haehling S, Katsiki N, Langlois M, Latkovskis G, Mancini GBJ, Mikhailidis DP, Mitchenko O, Moriarty PM, Muntner P, Nikolic D, Panagiotakos DB, Paragh G, Paulweber B, Pella D, Pitsavos C, Reiner Ž, Rosano GMC, Rosenson RS, Rysz J, Sahebkar A, Serban MC, Vinereanu D, Vrablík M, Watts GF, Wong ND, Rizzo M; International Lipid Expert Panel (ILEP). The role of nutraceuticals in statin intolerant patients. *J Am Coll Cardiol* 2018;**72**:96–118.
6. Cicero AFG, Colletti A, von Haehling S, Vinereanu D, Bielecka-Dabrowa A, Sahebkar A, Toth PP, Reiner Ž, Wong ND, Mikhailidis DP, Ferri C, Banach M; International Lipid Expert Panel. Nutraceutical support in heart failure: a position paper of the International Lipid Expert Panel (ILEP). *Nutr Res Rev* 2020;**33**:155–179.
7. Penson PE, Mancini GBJ, Toth PP, Martin SS, Watts GF, Sahebkar A, Mikhailidis DP, Banach M; Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group & International Lipid Expert Panel (ILEP). Introducing the 'Drucebo' effect in statin therapy: a systematic review of studies comparing reported rates of statin-associated muscle symptoms, under blinded and open-label conditions. *J Cachexia Sarcopenia Muscle* 2018;**9**:1023–1033.
8. Zhubi-Bakija F, Bajraktari G, Bytyçi I, Mikhailidis DP, Henein MY, Latkovskis G, Rexhaj Z, Zhubi E, Banach M; International Lipid Expert Panel (ILEP). The impact of type of dietary protein, animal versus vegetable, in modifying cardiometabolic risk factors: A position paper from the International Lipid Expert Panel (ILEP). *Clin Nutr* 2021;**40**:255–276.
9. Katsiki N, Mikhailidis DP, Bajraktari G, Miserez AR, Cicero AFG, Bruckert E, Serban MC, Mirrakhimov E, Alnouri F, Reiner Ž, Paragh G, Sahebkar A, Banach M; International Lipid Expert Panel (ILEP). Statin therapy in athletes and patients performing regular intense exercise—position paper from the International Lipid Expert Panel (ILEP). *Pharmacol Res* 2020;**155**:104719.
10. Banach M, Penson PE, Fras Z, Vrablik M, Pella D, Reiner Ž, Nabavi SM, Sahebkar A, Kayikcioglu M, Daccord M; FH Europe and the International Lipid Expert Panel (ILEP). Brief recommendations on the management of adult patients with familial hypercholesterolemia during the COVID-19 pandemic. *Pharmacol Res* 2020;**158**:104891.

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Weekly Journal Scan

A 'Once-and-Done' Approach to the Lifelong Reduction of Elevated Cholesterol

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Comment on 'In vivo CRISPR base editing of PCSK9 durably lowers cholesterol in primates', which was published in *Nature*, doi:10.1038/s41586-021-03534-y.

Key points

- CRISPR (clustered regularly interspaced short palindromic repeats)-related technologies are emerging therapeutic strategies to induce DNA modifications in humans. In this regard, gene editing of proprotein convertase subtilisin/kexin type 9 (PCSK9) might represent a promising approach for the prevention of coronary heart disease (CHD). The present study[1] investigates the impact of a single-nucleotide PCSK9 loss-of-function mutation by CRISPR adenine base editors (ABE) on low-density lipoprotein cholesterol (LDL-C) levels in non-human primates.
- To introduce a precise single-nucleotide PCSK9 loss-of-function mutation, a CRISPR ABE was delivered in macaques using lipid nanoparticles (LNPs). Adenine base editors of PCSK9 was confirmed in primary human hepatocytes, primary monkey hepatocytes, and mice.
- *In vivo* CRISPR ABE delivery led to a near-complete knockdown of PCSK9 in the liver after a single infusion of LNPs, with concomitant reductions in blood levels of PCSK9 and LDL-C of ∼90% and 60%, respectively. These changes were sustained for at least 8 months after a single-dose treatment. No relevant side effects were observed in the animals treated with a CRISPR editor-based strategy.
- Off-target gene editing was found at only one site in macaque liver, whereas no off-target editing was found in human hepatocytes.

Comment

Individuals with spontaneous loss-of-function PCSK9 mutations experience a significant reduction of both LDL-C levels (∼30–40%) as well as CHD risk (88%), and appear free from adverse clinical consequences.[2] Gene-editing technologies, which include the CRISPR–Cas nucleases and CRISPR base editor, have the potential to permanently modify disease-causing genes.[3] The demonstration of durable editing of PCSK9 in target organs is a key step before *in vivo* administration of specific gene editors in clinical trials. In this experimental proof-of-concept study, genetic inactivation of PCSK9 gene by CRISPR editors was associated with a substantial and sustained lowering of LDL-C levels in non-human

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