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Editorial

Cost-effectiveness with PCSK9 inhibitors: a matter of costs

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This editorial refers to 'Modelling the cost-effectiveness of PCSK9 inhibitors vs. ezetimibe through LDL-C reductions in a Norwegian setting', by M. Korman and T. Wisløff on page 15.

In this issue of the journal, Korman and Wisløff[1] present a study of the cost-effectiveness of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in a Norwegian setting. Because PCSK9 inhibitors are extremely expensive, such a cost-effectiveness analysis is very important. Specifically the authors compared the cost-effectiveness of PCSK9-inhibiting antibodies—using the costs of evolocumab—with that of ezetimibe by the use of a state-transition Markov model. Similar analyses have been reported recently from the US,[2,3] but it is important to obtain a European analysis because of the different prices and healthcare systems in Europe.

From their Norwegian model, the main conclusion of the authors is that PCSK9 inhibitors in general are too expensive despite the potential to lower LDL-cholesterol intensively.[4] As a rule, patients in primary prevention do not fulfil cost-effectiveness criteria. Only very high risk patients at older age exhibit acceptable cost-effectiveness numbers.

This generally negative conclusion could be altered significantly with a drop in price, as the authors illustrate very clearly in their table 5.[1] For the time being, however, it should be remembered that Norway has approved PCSK9 inhibitors but the reimbursement is strictly confined to patients with homozygous familial hypercholesterolaemia, which affects only ~10 patients in this country. This restrictive Norwegian reimbursement policy is remarkable because Norway is one of the richest countries worldwide.

In a broader context, it should not be forgotten that such an analysis is not a true evaluation but an estimation of effects based on the potential reduction of LDL-cholesterol. Recent outcome data from the FOURIER study suggest that such estimations may be too optimistic.[5] On the other hand, the basis for LDL-cholesterol reduction as a predictor of reduction of cardiovascular events is the calculation put forth by the Cholesterol Treatment Trialists' Collaboration (CTTC).[6] In such a context, the FOURIER data also look pretty congruent with what is to be expected by reduction of LDL-cholesterol, at least if the somewhat less reduced endpoints in the first year of treatment are not considered. Also what we do not know is if a short-term extensive reduction of LDL-cholesterol has some legacy effect as has been described, for example, for the WOSCOP study.[7]

In 1994, the 4S[8] demonstrated for the first time that lowering LDL-cholesterol by statins is worthwhile because it reduces total and coronary mortality as well as cardiovascular morbidity. This was confirmed by numerous further outcome studies. Later studies of high-intensity statins and of ezetimibe added to a statin have shown that even lower LDL-cholesterol is even better.[9,10] Now we know that lowest is best, as has been shown, for example, by FOURIER.[4] Thus, when considering cost-effectiveness, recommendations for the clinical cardiologist are clear: a stepwise treatment strategy should be used in lowering LDL-cholesterol consistent with the recent guidelines of the ESC: (i) use of the highest tolerated statin dose; (ii) addition of ezetimibe; and (iii) addition of PCSK9 inhibitors for the very high risk patient.[11]

The absolute risk of the patient and distance from the target of the LDL-cholesterol level will guide the clinician when to use a PCSK9 inhibitor. For example, a very high risk patient, post-myocardial infarction (MI) with diabetes mellitus and an LDL-cholesterol of, for example, 190 mg/dL (4.9 mmol/L) under the highest tolerated statin dose and also taking ezetimibe will be a very good candidate.

In a debate session at the last ESC meeting, the question of whether PCSK9 inhibitors should be used in post-MI patients was dealt with in a pro–con style. Dr Marc Sabatine (pro) and this editorialist (con) arrived at a consensus that PCSK9 inhibitors (i) are excellent tools to reduce LDL-cholesterol to unprecedented low levels; (ii) have a high degree of safety; (iii) can also significantly reduce cardiovascular non-fatal events; but (iv) no signal for mortality reduction could be seen in FOURIER; and (v) at present the costs are extremely high. Only a massive reduction of costs or a massive restriction of the agents to very, very high risk patients were deemed a solution. A recent Editorial came to a very similar conclusion.[12]

For the future, other methods to reduce PCSK9 such as inclisiran and other approaches that lower LDL-cholesterol such as anacetrapib could further foster the discussion.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal – Cardiovascular Pharmacotherapy* or of the European Society of Cardiology.

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Finally, much research is needed for the poorly determined state of statin intolerance which potentially is an important field for the use of PCSK9 inhibitors. Adherence to statins is a major challenge in modern lipid therapy, as recently discussed by our working group.[13]

Conflict of interest: H.D. reports lecture honoraria from Sanofi, Amgen, Boehringer Ingelheim, MSD, AstraZeneca, Bayer, BMS/Pfizer, and Janssen-Cilag, and has served on the advisory board of Sanofi, Amgen, Boehringer Ingelheim, MSD, and NovoNordisk, outside the submitted work .

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