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Role of combination therapy in treating raised LDL cholesterol in high-risk patients

Cholesterol carried in low-density lipoprotein cholesterol (LDL-C) and other apolipoprotein B-containing lipoproteins plays a causal role in atherogenesis,1–3 and, accordingly, is a key target in the prevention of atherosclerotic cardiovascular disease (ASCVD).2,3 Clinical trial evidence indicates that the magnitude of the benefit from LDL-C lowering is independent of the means by which it is achieved and is proportionate to the absolute decrease in lipoprotein level.1–4 Further, the relative risk reduction (RRR) appears the same, regardless of patient demographics and background medical history.1–4 Most guidelines (e.g. Piepoli et al.2016)2 recommend goals for LDL-C lowering that, while somewhat artificial and idealized constructs because the association between LDL-C and risk is continuous,1 have been useful clinically as a metric of therapeutic success. In clinical practice, however, not all patients achieve their LDL-C goal with statins alone, and increasing recognition of this treatment gap has led to the need to consider the routine use of combination lipid-lowering therapies.

The cholesterol absorption inhibitor ezetimibe added to statin achieves an incremental reduction in LDL-C of typically 20–25% and has been shown to provide a further decrease in ASCVD risk.5 Hence, this agent is now recommended for patients not achieving their lipid goal on maximum tolerated statin dose.2,5 Recently, the introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has made possible more profound LDL-C lowering of the order of 50–60%,6,7 and both currently marketed agents—evolocumab and alirocumab—have been approved for use in selected patient groups [those with severe ASCVD and those with primary hypercholesterolaemia, especially familial hypercholesterolaemia (FH)] with an inadequate response to maximally tolerated statin therapy or statin intolerance. With the publication of the FOURIER trial, we have evidence that the addition of PCSK9 inhibitors to statin delivers significant reduction in the risk of cardiovascular events, in line with the predicted benefit from meta-regression analysis.8

Cost-effectiveness analyses of PCSK9 inhibitor therapy

Although current European and US guidelines indicate that the use of PCSK9 inhibitors is appropriate in specific patients,9,10 uptake has been low, in most part due to their perceived expense.11 Cost-effectiveness analyses are essential in determining whether, how, and when PCSK9 inhibitor treatment meets accepted metrics of value for money. However, the different models published to date have produced widely varying and potentially confusing results. Eight reports on the health economics of PCSK9 inhibitor use have appeared: four academic-led12–15 and four supported by industry.16–19 Of these, three analyses were based on the FOURIER data.16,18,19 In addition, health technology appraisals were undertaken by the UK National Institute for Health and Care Excellence (NICE) for alirocumab and evolocumab.20

According to the US Institute for Clinical and Economic Review (ICER) analysis, the use of PCSK9 inhibitors did not meet a threshold of cost-effectiveness, defined in the study as $100 000 per quality-adjusted life year (QALY) gained, in patients with heterozygous FH
therapy. The baseline risk level corresponded to a total (initial plus recurrent) cardiovascular event rate of 6.4 per 100 patient-years.

Hernandez did not perform a cost-effectiveness analysis but calculated the societal impact of a health outcomes-based agreement whereby industry would not charge for PCSK9 inhibitors for those patients with events despite treatment.15 The author concluded that such a scheme would not lead to sufficiently low prices.

Assessments of alirocumab and evolocumab conducted by NICE indicated that these drugs could be cost-effective in the UK National Health Service setting.26 The approach assessed annual alirocumab costs of £4383 and starting LDL-C levels of 3.5 mmol/L for heterozygous FH patients with CVD and non-FH patients at very high risk, 4.0 mmol/L for non-heterozygous FH patients at high risk for CVD, and 5.0 mmol/L for heterozygous FH patients without CVD. LDL-C lowering was informed by the ODYSSEY trials,7 and the hazard ratio per 1.0 mmol/L reduction in LDL-C was estimated at 0.79.7 Example incremental costs per QALY gained for alirocumab were estimated as £37 000 (LDL-C > 4 mmol/L) for heterozygous FH primary prevention, £24 000 (LDL-C > 2.5 mmol/L) for heterozygous FH secondary prevention, £44 300 (LDL-C > 2.5 mmol/L) for patients with ‘high-risk’ CVD, and £34 000 (LDL-C > 2.5 mmol/L) for patients at ‘very high risk’.

There are noteworthy issues in the models described above. For example, Villa et al.18 assumed that the risk reduction of heart failure was the same as that of myocardial infarction. If that assumption is not made, the cost-effectiveness ratio increases to €62 000 per QALY. A further consideration is the treatment of stroke. In the report by Kazi et al.,15 the disutility applied to this outcome was surprisingly low, and because FOURIER found a significant stroke benefit from only 2 years of treatment,8 this would lead to an underestimate of cost-effectiveness.

However, as indicated by Toth et al.,17 the variation in outcome from these cost-effectiveness studies is driven (next to the assumed acquisition cost of the medicines) primarily by the estimation of absolute risk (of both first and recurrent events) rather than fundamental differences in modelling approach. Ongoing risk of future cardiovascular events is hard to define precisely for the populations of interest, given the dearth of long-term follow-up data in FH and the wide range of risk in subjects with established ASCVD.2,3,21 With the above economic results in mind, it seems more appropriate at the moment to base the use of these agents on a stratification of risk and benefit than to promulgate general deployment in secondary prevention.

### ‘Highest risk–highest benefit’ strategy to PCSK9 inhibitor use

The first element of a potentially useful ‘stratified-medicine’ strategy is to define ‘highest risk’, i.e. those with the highest baseline event rate. The level of risk required to justify the use of PCSK9 inhibitors will preclude their use in asymptomatic individuals without prevalent vascular disease (primary prevention), with the exception of FH with high LDL-C despite statin therapy, and so secondary prevention is the main focus. ‘Highest risk’ categories are polyvascular disease, ASCVD with co-morbidities such as chronic kidney disease or diabetes with end-organ damage or FH patients with a CVD event (Table 1).20–22 In this context, it would be worthwhile applying the
risk stratification tools as has been done for acute coronary syndrome patients with ezetimibe/statin combination therapy. The second element is to identify patients receiving the 'highest benefit'. Because the RRR is proportionate to the absolute decrease in LDL-C level in mmol/L, and the magnitude of percent LDL-C reduction with PCSK9 inhibitor therapy appears similar across baseline LDL-C subgroups, then patients with the highest starting LDL-C will achieve the greatest absolute reduction in LDL-C and hence the greatest RRR on the drugs.

Given the above, it is possible to construct a relatively simple matrix that provides a framework for optimizing the use of these agents. Figure 1 depicts the gradient of "number needed to treat" (NNT, over 5 years) based on the estimated risk of a future ASCVD event, the starting LDL-C, and the average RRR associated with a drug-induced LDL-C drop of 60%. Estimated NNT is lower (incremental cost-effectiveness ratio lower) in individuals with the greatest CVD risk and largest absolute LDL-C reduction. This is a conceptual expansion of the tables generated by NICE (in TA393 and TA394) and the approach advocated by Robinson et al.[22]

Depending on the prevailing price of PCSK9 inhibitors, bands of NNT that are payer-acceptable could be defined as an aid to prescribers—this is shown in the shaded green regions in Figure 1. For example, in the NICE alirocumab appraisal, it was calculated that, to

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**Table 1** Categories of ‘highest risk’ for ASCVD (around or above a benchmark of 30% 10-year risk) on statin therapy, based on published trial data

<table>
<thead>
<tr>
<th>Category, No CKD, Clinical ASCVD with CKD, Clinical ASCVD + diabetes</th>
<th>Projected 10-year risk on moderate- or high-intensity statin therapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical ASCVD + diabetes</td>
<td>28–38</td>
</tr>
<tr>
<td>No CKD</td>
<td>26–29</td>
</tr>
<tr>
<td>With CKD</td>
<td>28–43</td>
</tr>
<tr>
<td>Clinical ASCVD + CKD</td>
<td>34–35</td>
</tr>
<tr>
<td>Recent acute coronary syndrome (&lt;3 months)</td>
<td>32</td>
</tr>
<tr>
<td>CHD and poorly controlled risk factors</td>
<td>28–41</td>
</tr>
<tr>
<td>CHD and peripheral vascular disease</td>
<td>43–55</td>
</tr>
<tr>
<td>CHD and age ≥65 years</td>
<td>21–54</td>
</tr>
<tr>
<td>Stroke/transient ischaemic attack and male</td>
<td>31</td>
</tr>
<tr>
<td>CHD and familial hypercholesterolaemia (baseline LDL-C ≥190 mg/dL)</td>
<td>41</td>
</tr>
</tbody>
</table>

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease.

Adapted from Robinson et al.[22]
achieve the cost-effectiveness threshold of £30 000 per QALY gained, the baseline LDL-C level would need to be ~5.0 mmol/L for primary prevention in FH and ~3.5 mmol/L in very high-risk patients. Similarly, Robinson et al. showed that addition of a PCSK9 inhibitor provides a 5-year NNT ≤50 to prevent one cardiovascular event in very high-risk and high-risk patients with LDL-C ≥70 mg/dL and a 5-year NNT ≤30 for very high-risk and high-risk patients with LDL-C ≥130 mg/dL. It should be noted that in most health care systems, it is likely that the ‘prevailing price’ will need to be substantially below the list price for these drugs to be cost-effective in a broad range of target patient types (and greater transparency on drug discounts would aid decision-making). The strategy depicted in Figure 1 captures not only the potential clinical benefit for patient types at a given LDL-C level but also could be used to formulate the cost-effectiveness to society based on the range of NNT considered appropriate to an overall budget for these agents.

Conclusion

A simple strategy is needed to help physicians in the selection of patients suitable for PCSK9 inhibitor therapy, and we commend the ‘highest risk–highest benefit’ concept and advocate the development of simple aids (such as Figure 1) for clinicians to implement this framework. The aids should be adapted to the prevalent cost of these drugs in various pricing jurisdictions.

Authors’ contributions

All authors contributed to the conceptual background and content of the publication.

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