A review of health technology assessments (HTA) of PCSK9 inhibitors (PSCK9i) by ICER and NICE

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Introduction

- A high levels of LDL in the blood is a risk factor for cardiovascular disease (CVD).
- Standard lipid-lowering therapy involves statins which work by inhibiting an enzyme which is involved in intracellular cholesterol synthesis.
- PCSK9 is an enzyme involved in regulating degradation of LDLR.
- PCSK9 inhibitors function by preventing the degradation of LDLR, leading to increased internalization of LDL particles and decreased levels of LDL circulating in the blood.
- Two PCSK9 inhibitors, evolocumab (EVO; Repatha®; Amgen) and alirocumab (ALI; Praluent®; Sanofi/ Regeneron) are licensed for use by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The licensed indications are summarized in **Table 1**.

Table 1: Licensed indications for PCSK9 inhibitors[1-4]

Indication	Evolocumab		Alirocumab	
	FDA	EMA	FDA	EMA
To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease	✓	Not proven	Not proven	Not proven
As an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C).	✓	✓	✓	✓
As an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.	✓	✓	✗	✗

Table 2: Summary of HTAs for PCSK9 inhibitors[5-9]

PCSK9 inhibitors; ICER 2015	• In the 2015 assessment, ICER used an average cost for the two PCSK9 inhibitors ($14,350 (wholesale acquisition cost, WAC)) and estimated the effectiveness for reducing LDL-C and reducing risk of MI, CV death, and stroke from published sources. • The base case incremental cost-effectiveness ratio for a PCSK9 inhibitor + statin vs. statin alone was $302,000/QALY for patients with a prior history of CVD and LDL-C ≥70 mg/dL on statin therapy. • Based on an estimated uptake by 2.6 million patients over 5 years, ICER estimated an annualized budget impact of $21.4 billion in net health care cost growth over the first five years. ICER calculated that just 1% of eligible patients could be treated in order to avoid exceeding a budget impact threshold which caps the rate of healthcare spending growth at 1% higher than the growth in GDP. • Value based price benchmarking estimated that a price reduction of 85% on the list price would be needed to be cost-effective at common willingness-to-pay thresholds and to meet the budget impact threshold.
Evolocumab; ICER 2017	• Long-term data from the FOURIER trial for EVO showed a reduced risk of myocardial infarction (MI), stroke, and revascularization from year 1 to year 2, but a slightly increased risk of CVD related death. Risk of all-cause death was not reported. • In their reassessment of EVO, ICER used the WAC for EVO ($14,523) and modeled no effect on CVD death, resulting in a substantially higher cost per QALY gained than the 2015 assessment which had modeled a reduced risk of CV death. • The base case incremental cost-effectiveness ratio for EVO + statin vs. statin alone was ~$1.34million/QALY. • Value based price benchmarking estimated that discounts of 85% to 88% would be required to make EVO cost-effective at common willingness-to-pay thresholds of $150,000 and $100,000 per QALY.

Alirocumab; ICER 2018	• Long-term data from the ODYSSEY Outcomes trial for ALI demonstrated reduced risk for a composite outcome of CVD death, MI, stroke, and unstable angina, as well as all-cause death from year 1 to year 2.
	• The ICER reassessment used the WAC for ALI ($14,560) and assessed two scenarios:
	  • Modeling the observed reduction in risk of CV events: incremental cost-effectiveness ratio for patients with LDL-C ≥100 mg/dL was $164,006/QALY for ALI + statin vs. statin alone.
	  • Modeling this risk plus the observed reduction in risk of all-cause mortality: the incremental cost-effectiveness ratio was $135,137/QALY for ALI + statin vs. statin alone.
	• Value based price benchmarking estimated that in these two scenarios price discounts of 45% to 70% would be required to meet the common willingness-to-pay thresholds of $150,000 and $100,000 per QALY.

Evolocumab and Alirocumab; NICE 2016	• NICE assessments considered EVO or ALI + ezetimibe + statin vs. ezetimibe + statin.
	• On the basis of most plausible incremental cost-effectiveness ratios below £30,000 (~$40,000) per QALY, NICE recommended both PCSK9 inhibitors for the following subpopulations with elevated LDL-C despite maximum tolerated lipid-lowering therapy:
	  • Primary non-familial hypercholesterolemia or mixed dyslipidemia in adults with a high risk of cardiovascular disease and persistent LDL-C levels of at least 4.0 mmol/L.
	  • Primary non-familial hypercholesterolemia or mixed dyslipidemia in adults with a very high risk of cardiovascular disease and persistent LDL-C levels of at least 3.5 mmol/L.
	  • Heterozygous-familial hypercholesterolemia in adults without a history of cardiovascular disease and persistent LDL-C levels of at least 5.0 mmol/L.
	  • Heterozygous-familial hypercholesterolemia in adults with a history of cardiovascular disease and persistent LDL-C levels of at least 3.5 mmol/L.
	• NICE found that incremental cost-effectiveness ratios for patients with lower LDL-C concentrations or with primary non-familial hypercholesterolemia without CVD exceeded the £30,000 (~$40,000) willingness-to-pay threshold.
	• The recommendations relied on a patient access scheme involving a confidential discount on the list prices. List prices per year at time of assessment were £4,422.60 (~$5,900) for EVO and £4,383 (~$5,850) for ALI (GBP to USD conversions made at June 2016 exchange rate obtained from poundsterlinglive.com; 1 GBP = 1.3346 USD).

Objectives and methods

- To search the websites of the Institute for Clinical and Economic Review (ICER; USA; https://icer-review.org) and the National Institute for Health and Care Excellence (NICE; UK; https://www.nice.org.uk) to identify HTAs of EVO and ALI.
- To perform a detailed review of available HTA documents.
- To identify the methods of evaluation, outcomes, and key decision drivers.
- To consider the impact of these assessments on patient access.

Results

- PCSK9 inhibitors were initially subject to a joint assessment by ICER in 2015[5]. EVO (TA394) and ALI (TA392) underwent separate assessments by NICE in 2016[6,7].
- Subsequent reassessments have been made by ICER of EVO in 2017[8], and ALI in 2018[9], following availability of long-term clinical data. HTAs are summarized in **Table 2**.

Conclusions

- The influence of the 2015 ICER review on US payer perceptions is unclear, however barriers to access including exclusion from insurance plans, requirement for prior authorization, and unclear requirements for numbers of prior statin failures cause rejection of high proportions of PCSK9 inhibitor prescriptions by US payers[10].
- The result is that physicians may be unable to treat their patients with the drugs that they believe are most likely to be effective. Initiatives such as the American Society of Preventive Cardiology (ASPC) app aim to aid prescribers meet the strict requirements of US payers.
- The recent ICER reassessment of EVO has highlighted that the risk of CVD death increased in years 2+ compared with year 1 and suggested that substantial price discounts would be required to meet willingness-to-pay thresholds, which may further negatively influence payers. The reassessment of ALI is unlikely to improve access without substantial price discounts, despite a reduction in risk of death.
- Guidance for both PCSK9 inhibitors are scheduled for review by NICE during 2018, following availability of longer-term RCT data including the landmark analyses for individual outcomes. Trial results for EVO, which did not show reduced CVD death, and use of a composite endpoint for ALI may cause challenges during NICE reassessment.
- Price discounts have proved effective in securing reimbursement for PCSK9 inhibitors in the UK. In the US, prices are considerably higher than the UK, and ICER have reported that substantial discounts are required to make the drugs affordable. Outcome based refund schemes, such as that offered by Amgen[11] may help US payers to manage the risk associated with the potentially large budget impact, although these may be difficult to implement and may not be an approach which is favored by all payers[12].
- In the US, the size of the patient population which is potentially eligible for PCSK9 inhibitors means that payers may view the potential budget impact as unmanageable at current prices. In the UK, access to PCSK9 inhibitors is restricted to patient subgroups who are at the greatest risk of CVD or for whom statin treatment is not effective, reducing the size of the eligible patient population.

References:
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