A study in high risk, maximally pre-treated patients to determine the potential use of PCSK9 inhibitors at various thresholds of total and LDL cholesterol levels

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Keywords: PCSK9 inhibitors, statins, ezetimibe, dyslipidaemia targets

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Conflict of interest: No conflicts of interest. No financial support.

Funding: none

Word count: paper: 1342, abstract: 243

Abstract:

Purpose of the study:

Statins and ezetimibe reduce low density lipoprotein cholesterol (LDL-c) and cardiovascular disease (CVD) risk. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors lower LDL-c by 50-70% and might be useful in refractory patients. The National Institute for Health and Care Excellence (NICE) technology appraisal guidance (TAG) recommends use of these drugs in secondary prevention and familial hypercholestrolaemia (FH) at differing LDL-c thresholds. We have estimated the proportion of patients in whom this third-line drug might be useful.

Study Design:

We used data from a lipid lowering audit programme to study 72 with FH and/or CVD of 271 patients referred over 12 months who failed to achieve target total cholesterol (TC) and LDL-c levels. All 72 patients were treated with ezetimibe, 69 cases also received statins. We used LDL-c thresholds 1.5-5.5mmol/l to estimate how many of these refractory patients could benefit from PCSK9 inhibitors.

Results:

In the 72 patients, TC and LDL-c targets were not met by 64 and 53 patients respectively. We judged using the NICE TAG, that only 1 patient (1.4% ezetimibe requiring and 0.4% total referrals) required a PCSK9 inhibitor.

Conclusion:

We determined that the proportion of patients eligible for a PCSK9 inhibitor at various TC and LDL-c levels is modest. This may reflect the use of all available statins in UK lipid clinics often at non-daily frequency. We suggest that cost effective use of PCSK9 inhibitors requires prescribing being restricted to clinicians working in specialised lipid clinics.

Introduction:

The association between cardiovascular disease (CVD) risk and raised serum total cholesterol (TC) and low density lipoprotein-cholesterol (LDL-c) has been demonstrated in epidemiology studies [1,2] and, intervention trials showing significant decreases in CVD following use of LDL-c reducing agents such as statins and ezetimibe. Following the Scandinavian Simvastatin Survival Study (4S) in 1994, statins have been the mainstay of lipid lowering treatments [3].

Since 1998 various secondary prevention targets have been proposed based on interventional trials [4-11]. As a result, the Quality and Outcomes Framework, a UK primary care incentive scheme, has introduced targets of TC <5mmol/l and LDL-c <3mmol/l [12]. Further, lower targets that also include non-high density lipoprotein–cholesterol (HDL-c) have been presented by the Joint British Society in 2014 [13]. These indicate a non HDL-c target of <2.5mmol/l (considered equivalent to a LDL-c <1.8mmol/l).

However, despite the increasing efficacy of the newer statins, many patients do not achieve LDL-c targets [14]. The introduction of ezetimibe in 2002 offered a further treatment route [15,16]. Intervention trials with ezetimibe (used with statins) such as SHARP and IMPROVE-IT led to CVD benefits in keeping with LDL-c reduction and suggested that LDL-c reduction, regardless of treatment will effect a reduction in CVD [17,18].

However, even with combination treatment, some patients fail to achieve targets. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are monoclonal antibodies that inactivate PCSK9 leading to decreased LDL receptor degradation and increased LDL uptake. Alirocumab and evolocumab were licensed in 2015 and, given as monotherapy or with statins effected LDL-c reductions of 50-70% [19,20]. However, with an annual UK cost of over £4000/patient (both agents), the affordability of these drugs had been questioned. Following an undisclosed price discount (both drugs) the technology appraisal guidance (TAG)

(https://www.nice.org.uk/guidance/ta393, https://www.nice.org.uk/guidance/ta394) issued by NICE recommends use of PCSK inhibitors (in the event of provision at a discounted price) in secondary prevention and heterozygous familial hypercholestrolaemia (FH). In secondary prevention LDL-c treatment thresholds of 4.0mmol/l and 3.5mmol/l are recommended in patients considered high risk (history of acute coronary syndrome, coronary or other arterial revascularisation procedures, chronic heart disease, ischaemic stroke, peripheral arterial disease) and very high risk (recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed) of CVD respectively, following the use of maximally tolerated statins and ezetimibe. In contrast, a LDL-c threshold >5.0mmol/l was recommended in FH after statin/ezetimibe treatment.

There is little data from routine care on the numbers of patients who do not meet lipid targets following maximal treatment. In 2009 we carried out a case-note audit estimating the efficacy of ezetimibe and now describe the use of these data to estimate the number of patients in a secondary care out-patient clinic who might be suitable for treatment with a PCSK9 inhibitor at different cut-off levels.

Materials and Methods:

The Lipid and Metabolic Clinic in the Heart of England Foundation NHS Trust serves a primary care catchment of 440,000 people and treats patients not achieving target lipid levels and/or experiencing side effects from lipid lowering therapy (Figure 1). In our NHS region neither rosuvastatin nor ezetimibe can be prescribed in primary care without local lipid clinic recommendation. Between April 2007-March 2008, 271 patients were referred to the Clinic and 72 of these patients were started on ezetimibe when not achieving target TC and/or LDL-c levels on maximal statin treatment (Table 1). Data on these patients were collected as part of the lipid clinic audit programme carried out by the Department of Clinical Biochemistry, Heart of England Foundation NHS Trust to evaluate guideline compliance and efficacy of lipid lowering agents (statins, fibrates,

ezetimibe) [21,22]. In the clinic we tried to achieve targets of TC: 4mmol/l and/or LDL-c: 2mmol/l. Treatment preceded the NICE guidance for FH management in 2008 (https://www.nice.org.uk/guidance/cg71). Table 1 shows treatment details in these patients.

TC, TG and HDL-c levels were measured using the Roche Modular platform P800 analyser with Roche reagents in the Department of Clinical Biochemistry at Good Hope Hospital. LDL-c was calculated on the laboratory computer system when TG levels were <4.5mmol/l. The audit data was transferred from an Excel spread sheet to Stata version 8 (College Station, TX) and patient distribution of TC and LDL-c levels post-statin and/or ezetimibe treatment calculated.

Results

Table 1 shows changes in lipids following treatment in the total cohort and sub-groups. In the total group (n=72) mean TC, pre-treatment (post lifestyle intervention) was 8.5mmol/l and mean LDL-c (available in only the 63 patients who did not have elevated TG levels) was 5.6mmol/l. Following treatment, mean TC and LDL-c decreased to 4.8mmol/l (44% reduction) and 2.5mmol/l (55% reduction) respectively.

Table 2 shows that 64 and 53 patients did not attain clinic targets of TC (4mmol/l) and LDL-c (2mmol/l) respectively. The table indicates the proportion of patients who would be eligible for a PCSK9 inhibitor at different TC and LDL-c thresholds; LDL-c of 2mmol/l, 19.6% of referred patients, LDL-c of 3mmol/l, 5.2%, LDL-c of 4mmol/l, 1.5% and LDL-c threshold of 5mmol/l, 0.4% of total referrals.

Of the 34 patients with definite/probable FH only 1 individual did not meet the LDL-c target of 5mmol/l as in the NICE TAG. Of this group 6 patients had established CVD, all with LDL-c <3.0mmol/l. All 44 patients with established CVD (38 not satisfying the criteria for FH) had LDL-c <3.5mmol/l. Thus, only 1 patient would have required the addition of a PCSK9 inhibitor based on the NICE TAG.

Discussion:

We used data collected in 2009 from a clinical audit on ezetimibe efficacy to estimate using different TC and LDL-c thresholds, the numbers of patients who might be eligible for a PCSK9 inhibitor. This audit has limitations; patient numbers were small and they were seen because of clinical need and not a study protocol. However, decisions on PCSK9 inhibitor use will need to be compatible with an out-patient setting. Thus, we suggest our approach is valid.

The critical role of LDL-c in determining risk is shown by meta-analysis of 14 trials comprising 90,000 individuals; LDL-c reduction of 1mmol/l conferred a reduction in relative coronary heart disease risk of 23% [23]. Further, the additive effect of combinations of drugs that reduce LDL-c levels by different mechanisms is shown by IMPROVE-IT [23]. A meta-analysis (7 trials, 31,048 patients) by Saverese et al. suggested addition of ezetimibe significantly reduced myocardial infarction and stroke, but not overall and cardiovascular mortality [24].

PCSK9 inhibitors are effective; they lower serum LDL-c levels by 50- 70% [19,20] and reduce myocardial infarction and all-cause mortality [25]. Clearly, while PCSK9 inhibitors might be effective, their cost demands consideration of which patients should receive them. In particular, the relationship between baseline LDL-c, the extent of LDL-c reduction and health benefit needs consideration.

Our data suggest patient numbers eligible for PCSK9 inhibitors are modest. There are various reasons for this. All patients attended the lipid clinic and all available statins were tried. Many patients were prescribed statins with long half lives at non-daily frequency. Some patients purchased co-enzyme Q10 supplements and reported improved statin related tolerability. This suggests that all prescribing of PCSK9 inhibitors should be via specialist lipid clinics.

Study limitations include the small sample size and lack of outcome data. Further, we could not stratify our patients as high or very high risk as defined by NICE. We speculate that there would be an accumulating cohort of patients not having met LDL-c levels over many years who will require PSCK9 inhibitors soon after the NICE final approval. Once these patients are treated we expect new prescriptions to fall to the figures described in this study.

Clearly, current guidance on PCSK9 usage is based on limited information on efficacy and adverse effects and, no outcome data (eg. CVD/mortality) is available. Thus, randomised controlled studies and longitudinal observational studies are required with CVD/mortality as end-points. It is also important that benefits in conditions not specified by NICE, such as individuals with metabolic syndrome/type 2 diabetes are also evaluated. Adverse event data must be collected from trials and routine use. Once these are available re-evaluation of LDL-c thresholds in various high risk patients can be carried out.

Main messages

- The number of patients requiring third-line treatment with a PCSK9 inhibitor appears to be small.
- Effective clinical use and cost efficiency is best achieved by restricting PCSK9 inhibitor prescribing to clinicians specialising in treating dyslipidaemia.
- While use of PCSK9 inhibitors may be relatively large initially, once the backlog of patients currently requiring third-line intervention is cleared, prescribing will fall as only newly diagnosed patients will require treatment.

Current research questions

- Outcome studies of PCSK9 inhibitor treatment with CVD/mortality as end-points are needed.
- Adverse effects of PCSK9 inhibitors need be assessed in routine clinical use.
- Efficacy and CVD outcomes in patients not currently specified by NICE (eg. Metabolic syndrome/type 2 diabetes) require study.

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Table 1: Results (mean, range) from 72 patients pre (no lipid lowering therapy) and post (after maximal lipid lowering) treatment. Ezetimibe was combined with a statin in 60 patients, statin and a fibrate in 9 patients whilst 3 patients were on ezetimibe monotherapy due to statin intolerance.

	Cholesterol (mmol/l)		TG (mmol/l)		HDL-c (mmol/l)		LDL-c (mmol/l)*	
	pre	**post**	**pre**	**post**	**pre**	**post**	**pre**	**post**
All patients (72)	8.5 (5.2-14.0)	4.8 (3.2 – 7.1)	3.0 (0.6-18.5)	1.7 (0.6 – 4.3)	1.5 (0.7-2.8)	1.6 (0.6 – 3.1)	5.6 (3.9 - 11.8)	2.5 (1.0 – 5.1)
Patient subgroups								
Male (44)	8.1 (5.2 - 11.9)	4.7 (3.2-6.7)	4.3 (1-18.5)	1.8 (0.8-4.3)	1.2 (0.7-1.9)	1.3 (0.6-2.2)	5.2 (3.9-9.9)	2.6 (1.4-5.1)
Female (28)	8.8 (6.2 – 14.0)	4.9 (3.7-7.1)	2.2 (0.6-5.5)	1.6 (0.6-3.3)	1.7 (1.0-2.8)	1.8 (1.1-3.1)	5.8 (3.9-11.8)	2.4 (1.0-4.5)
Diabetes (9)	7.8 (6.2-10.0)	4.5 (3.7-5.4)	3.1 (1.0-5.1)	2.3 (0.9-2.2)	1.3 (0.9-1.9)	1.5 (0.9-2.2)	5.0 (4.0-6.7)	2.0 (1.0-3.1)
FH (34)	9.7 (6.7-14.0)	5.2 (4.1-7.1)	2.0 (0.8-5.5)	1.6 (0.6-3.0)	1.6 (1.1-2.6)	1.7 (1.0-2.3)	6.7 (4.7-11.8)	2.8 (1.4-5.1)
FH – primary prevention (28)	9.8 (6.7-14)	5.3 (4.1-7.1)	2.1 (0.8-5.5)	1.5 (0.6-3.0)	1.6 (1.1-2.6)	1.7 (1.0-2.3)	6.8 (4.8-11.8)	3.0 (1.4-5.1)
FH – secondary prevention (6)	9.1 (7.3-11.3)	4.9 (4.6-5.4)	2.0 (1.2-3.1)	1.7 (0.8-2.9)	1.7 (1.2-2.3)	1.8 (1.3-2.2)	6.3 (4.7-8.3)	2.3 (1.6-2.9)
Non – FH secondary prevention (38)	7.5 (5.2-11.9)	4.5 (3.2-5.7)	3.8 (0.6-18.5)	1.9 (0.7-4.3)	1.4 (0.7-2.8)	1.5 (0.6-3.1)	4.7 (3.9-6.7)	2.2 (1.0-3.1)
Atherogenic lipoprotein phenotype (13)	7.7 (5.2-11.9)	4.7 (3.8-6.7)	3.6 (1.7-10.2)	2.2 (1.2-4.3)	1.0 (0.7-1.2)	1.1 (0.6-1.4)	5.1 (3.9-9.9)	2.6 (1.9-5.1)
Patients on statin/ezetimibe (60)	8.6 (6.1-14.0)	4.9 (3.2-6.7)	2.3 (0.6-10.2)	1.6 (0.6-4.3)	1.6 (0.9-2.8)	1.7 (0.9-3.1)	5.8 (2.8-11.8)	2.5 (1.4-5.1)
Patients on ezetimibe/fibrate +/- statin (9)	7.7 (5.2-11.9)	4.2 (3.7-5.0)	7.7 (4.6-18.5)	2.1 (1.2-2.8)	1.0 (0.7-1.7)	1.2 (0.6-1.8)	N/A	2.0 (1.0-2.7)

* LDL-c was calculated in patients with TG < 4.5mmol/l.

ezetimibe monotherapy results (n=3): TC: pre = 8.1mmol/l, post = 5.6mmol/l, LDL-c: pre = 4.8mmol/l, post = 3.2mmol/l

Table 2: Numbers and proportions of patients not meeting various TC and LDL-c levels.

	patients not achieving TC and LDL-c levels		
TC (mmol/l)	**patient numbers**	**% of 72 study patients**	**% of 271 total referrals**
3	72	100.0	26.6
3.5	71	98.6	26.2
4	64	88.9	23.6
4.5	50	69.4	18.5
5	26	36.1	9.6
5.5	13	18.1	4.8
6	6	8.3	2.2
6.5	2	2.8	0.7
7	1	1.4	0.4
8	0	0.0	0
LDL-c (mmol/l)			
1.5	66	91.7	24.4
2	53	73.6	19.6
2.5	34	47.2	12.5
3	14	19.4	5.2
3.5	6	8.3	2.2
4	4	5.6	1.5
4.5	1	1.4	0.4
5	1	1.4	0.4
5.5	0	0.0	0.0

Figure 1: Outline of the pathway (QoF and NSF targets) that resulted in referral to the secondary care lipid clinic and audit of TC and LDL-c achieved following maximal current lipid lowering agents.