Audit of PCSK-9 Inhibitor Prescribing in GGC: Real Patient Data

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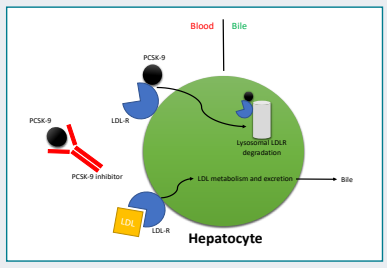
BACKGROUND

There is a clinical need for additional lipid-lowering therapies

- Low-density lipoprotein (LDL) reduction improves cardiovascular outcomes in primary and secondary prevention populations, especially in Familial Hypercholesterolaemia (FH).
- Statins and ezetimibe are the mainstay of therapy, but are limited by side-effects and efficacy.

Figure 1. Simplified mechanism of action of PCSK-9 inhibitors

- *PCSK-9 is secreted by hepatocytes and tags LDL receptors (LDLR) for lysosomal degradation.*
- *PCSK-9 inhibitors are monoclonal antibodies which act as extracellular decoy receptors for PCSK-9, preventing lysosomal LDLR degradation.*
- *Greater hepatocyte LDLR expression increases LDL clearance and lowers serum LDL.*



PCSK-9 inhibitors lower LDL and improve cardiovascular outcomes

- The FOURIER and ODYSSEY trials demonstrated LDL reduction and fewer cardiovascular events in evolocumab and alirocumab treated patients respectively.

PCSK-9 inhibitors currently in clinical use

- Alirocumab 75mg or 150mg subcutaneously every 2 weeks
- Evolocumab 140mg subcutaneously every 2 weeks

Current GGC criteria for prescription

PCSK-9 inhibitors are expensive and lack long-term safety data, hence strict criteria for use:

1. Prescribed only in a specialist lipid clinic
2. Genetically proven FH
3. Uncontrolled hyperlipidaemia on maximally tolerated statin and ezetimibe (LDL > 5.0mmol/L in primary prevention and LDL > 3.5mmol/L in secondary prevention).

AIMS OF AUDIT

- What are the demographics and indications for use in those prescribed PCSK-9 inhibitors?
- Are current prescribing guidelines adhered to?
- Are PCSK-9 inhibitors safe and effective in the GGC population?

METHODS

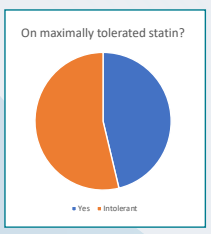
80 patients prescribed PCSK9 inhibitors were identified from lipid clinics at four sites within GGC: Glasgow Royal Infirmary (GRI), Royal Alexandra Hospital, Paisley (RAH), West Ambulatory Care Hospital (ACH) and Queen Elizabeth University Hospital (QEUH).

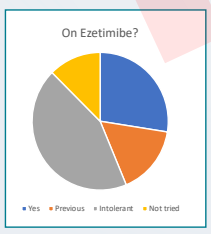
Data was collected from July 2017 – September 2020.

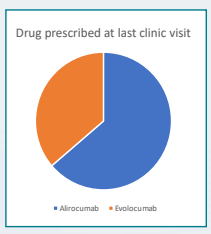
RESULTS

Demographics

In those prescribed PCSK-9 inhibitors, 55% were male and 45% were female. The mean age was 61 years. Realistic medicine appears to have been observed; only 3% patients prescribed PCSK-9 inhibitors were aged 80 or older.







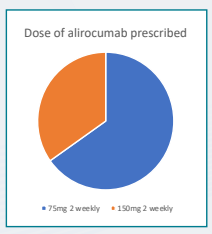
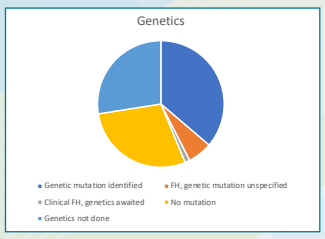


Figure 2 – Prescribed lipid-lowering therapies

- *All patients had tried a statin.*
- *At time of prescription, 46% were taking their maximally tolerated statin; 54% were intolerant to more than one statin.*
- *28% patients were taking ezetimibe. 44% were intolerant to ezetimibe, 16% stopped ezetimibe on starting PCSK-9 inhibitor., and 13% had not tried ezetimibe.*
- *63% (n=46) were prescribed alirocumab; 37% (n=27) were prescribed evolocumab.*
- *At latest clinic visit, of those prescribed alirocumab, 65% were taking the lower dose (75mg) and 35% had been increased to the higher dose (150mg).*

Figure 3 – Genetics

- *36% (n=29) patients prescribed PCSK9 inhibitors had genetic studies confirming FH, the majority of which had LDLR mutations (n=23), with the remainder having ApoB mutations (n=5) or Familial Defective Betalipoproteinaemia (n=1).*
- *6% (n=5) had a diagnosis of genetically confirmed FH without genetics specified and 1% (n=1) had genetic studies taken but results awaited.*
- *29% (n=23) patients had no mutation identified on genetic testing.*
- *28% (n=22) patients did not have genetic testing undertaken.*



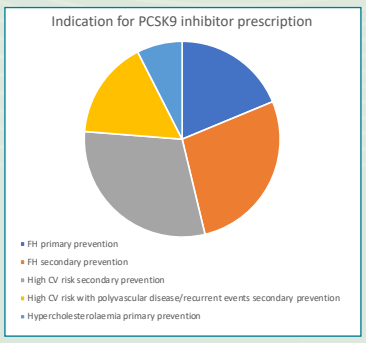


Figure 4 - Indications for use

19% (n=15) were prescribed for FH primary prevention, 28% (n=22) for FH secondary prevention, 30% (n=24) for high cardiovascular risk secondary prevention, 16% (n=13) for high cardiovascular risk with polyvascular disease or recurrent events secondary prevention, and 8% (n=6) for primary prevention in hypercholesterolaemic patients.

Adverse Effects

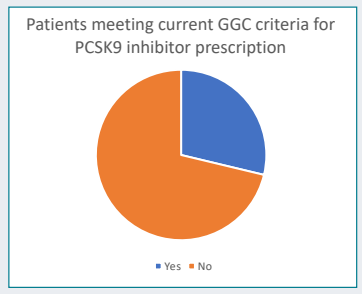
67% patients taking alirocumab and 61% of patients taking evolocumab reported no side-effects. Injection-site reactions and flu-like symptoms were the most commonly reported; side-effects were otherwise idiosyncratic.

9% (n=7) patients stopped taking PCSK-9 inhibitors (alirocumab n=4; evolocumab n=3) at time of audit; 6 of whom due to adverse effects and 1 due to invalid indication for use. 5 patients switched from evolocumab to alirocumab due to adverse effects (n=4) or inadequate response (n=1).

Adverse effects leading to cessation included: flu-like symptoms (n=1); headache, neck pain and multiple viral infections (n=1); unilateral leg vasculitis and haemosiderin deposition (n=1); lower limb twitches, paraesthesia, muscle pain and weakness (n=1); tiredness and bilateral leg pain (n=1); exacerbation of COPD (n=1). Aside from flu-like symptoms, it is unclear the extent to which symptoms can be attributed to PCSK-9 inhibitor use.

Figure 5 - Compliance with GGC guidelines

- *Only 29% (n=23) of patients prescribed PCSK-9 inhibitors met prescription criteria.*
- *If access was widened to include high-risk secondary prevention non-FH patients (LDL > 4mmol, or LDL > 3.5mmol in those with recurrent events or polyvascular disease), 56% (n=45) of patients would have met prescription criteria.*
- *Other reasons for not meeting criteria included: no genetic studies taken (2%; n=1), ezetimibe not tried (12%; n=7), prescribed for primary prevention only (11%; n=6) and LDL levels below criteria for prescription (26%; n=21).*



Compliance by site

The percentage of patients in each area meeting current GGC criteria for PCSK9 inhibitor prescription was 33% at Glasgow Royal Infirmary (GRI), 62% at Royal Alexandra Hospital Paisley (RAH), 19% at West Ambulatory Care Centre (West ACH) and 31% patients at Queen Elizabeth University Hospital (QEUH).

RAH was the only centre to prescribe PCSK-9 inhibitors appropriately in the majority of patients.

Efficacy

Data collected from this audit was not a controlled trial. Concomitant lipid-lowering therapies, compliance and demographics were not accounted for, and there was no inclusion criteria or control group. Nevertheless, observational data here demonstrates a similar reduction in LDL cholesterol to trial data.

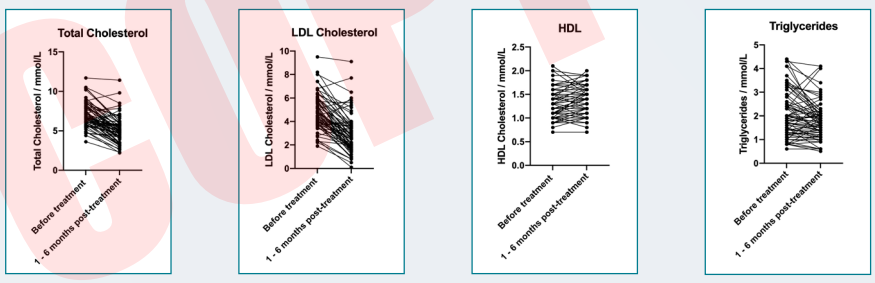


Figure 6 – Efficacy within 6 months

In 69 patients who had comparable data (i.e. had a repeat full lipid profile and attended follow-up), when measured 1-6 months after treatment initiation:

- *Total cholesterol fell by a mean 28% (7.10mmol/L to 5.10mmol/L); p<0.001 Wilcoxon test*
- *LDL cholesterol fell by a mean of 40% (4.85mmol/L to 2.92mmol/L); p<0.001 Wilcoxon test*
- *HDL and triglycerides were similar (not analysed as not necessarily fasted samples)*

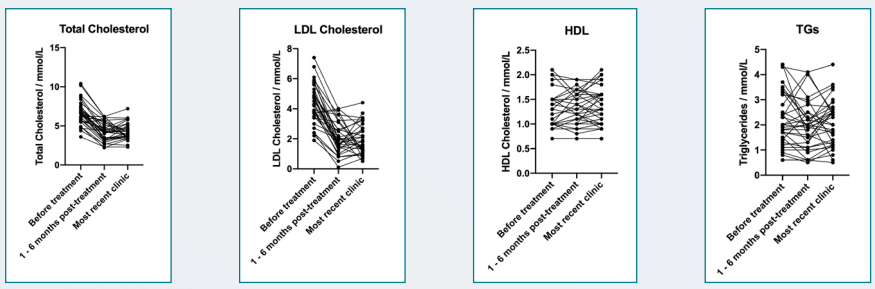


Figure 7 – Ongoing efficacy

In a subset of 33 patients who had comparable data (did not change drug or stop therapy, attended more than one follow-up with full lipid profiles, average treatment duration 22 months)

- *Total cholesterol fell by a mean of 35% within 1-6 months (6.64mmol/L to 4.29mmol/L), and a total mean reduction of 36% at last clinic visit (4.26mmol/L).*
- *LDL cholesterol fell by a mean of 52% within 1-6 months (4.31mmol/L to 2.10mmol/L), and a total mean reduction of 54% at last clinic visit (1.96mmol/L).*
- *Despite individual variation, maximal effect appears to occur on average within 6 months, and treatment effect is maintained thereafter.*

CONCLUSIONS

- PCSK-9 inhibitors are effective lipid-lowering agents and largely well tolerated in the GGC population, but long-term safety and efficacy data for PCSK-9 inhibitors is lacking.
- PCSK-9 inhibitors appear to lower LDL by 40% on average within 6 months of use.
- PCSK-9 inhibitors are mostly prescribed against current guidelines in GGC.
- Guidelines under consideration to widen access to non-FH high-risk secondary prevention patients with uncontrolled hyperlipidaemia would improve compliance to guidelines.
- Under-review LDL targets (<1.8mmol/L in secondary prevention and risk stratified but at least <3.0mmol/L in primary prevention), if applied to PCSK-9 inhibitors, would also widen access.
- In the meantime, clinicians should ensure genetic studies for FH have been undertaken, all patients should have tried ezetimibe prior to PCSK-9 inhibitor prescription, PCSK-9 inhibitors should not be prescribed for primary prevention, and those with adequately low LDL levels on conventional therapy should not be prescribed PCSK-9 inhibitors.
- Patients should be followed up within 6 months and have a full lipid profile taken to allow assessment of treatment response.

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