Mastering cholesterol to optimise CVD prevention webinar series

Targeting lipids: A primary and secondary care perspective (26 Jan 2023)

Q&A with Dr Sue Kemsley (SK) and Dr Gavin Galasko (GG)

Question 1

Is there any evidence that starting statins in over 84yr olds actually prolongs or adds to the quality of life?

SK: I'm afraid I can't quote any evidence to you; I'm sure there's some out there. I think what's really important is not the age and number, and what I've said in my slides is that people over the age of 84 are automatically at high risk of cardiovascular disease. That doesn't necessarily mean that they should all have lipid therapies, of course. But age is just a number isn't it; there are plenty of younger people who might have severe multi-morbidity, end of life conditions, frailty, that it wouldn't make sense to commence lipid therapies. So I think that we need to be careful of treating age as a number and there may be people who are extremely fit and well, very active and actually you don't want them to have a stroke, which is disabling and will result in dependency, requirement of social care and increased use of the healthcare system, of course. So, I think age is not a number; I do think we need to be careful though, as people get older, in ensuring that decisions are right for the patient, so I think it is to discuss with the patient. As to the evidence, I'm afraid I can't quote you. I'm sure there is some there; I'm not sure whether Gavin might know the answer to that.

GG: What I would first say is that at the age of 85, the life expectancy average is still six years. And so there will be healthy 84 year olds and unhealthy 84 year olds. So, there is life to protect and as Sue said, statins can lower your annual risk by over 25%, so there is direct theoretical benefit. The research studies haven't recruited loads of people in their 80s; there are some that have recruited people over 75, some over 80, and benefit has been seen in that age range, certainly, but numbers are quite small. But I think it's a patient by patient basis. Frail people with co-morbidity and poor life expectancy, you probably want to be giving them the quality of life. People who are actually quite fit, they would be protected more and have more to gain, and I would do it on a case by case basis.

Question 2

At what age would you be having discussions with patients about de-prescribing statins?

SK: I think that's a conversation to have with the patient. I think it can make people very nervous when you withdraw their therapies. I don't think that we should say that, you know, at the age of 86 we should definitely stop. I think again it has to be tailored to the patient; it has to be a conversation. At the end of the day, we don't want them to have a disabling heart attack or stroke that's going to land them in a nursing home. But, if they've got multi-morbidity already, maybe we need to be a little more pushy on saying, actually this drug is unlikely to be benefitting you now.

Question 3
QRISK2 and QRISK3 - does it make much difference which one to use?

GG: It doesn't make much difference which one to use. The old guidelines mention QRISK2, the new guidelines almost certainly will mention QRISK3. I think QRISK3 is slightly better and if you've got access to that, use that. If you've only got access to QRISK2, use that. They're both very validated. There are likely to be more scores that come out and there are other, newer tests coming out all the time. But at moment I would say QRISK3 if you've got it; that will come out I'm sure in the summer to be released with the NICE new lipid guidelines. But if you've got access to QRISK2 that's absolutely fine and not much different.

Question 4
Are you concerned about removal of QRISK calculator from EMIS in March 2023?

SK: I am indeed. I'd just like to add a bit about QRISK. I think that if you do a QRISK2, the benefit at the moment and the current situation is that QRISK2 is embedded in GP systems, so it's really easy to use. If you do a QRISK2 and a patient has a QRISK of over 10%, you can take it as red that the patient is high risk. The only thing that QRISK3 will do is add a little bit more to that, so in other words, if the patient has a QRISK2 score of just below 10%, you might want to consider doing a QRISK3 if you're really keen on starting lipid therapies, as that will probably take them over the 10% threshold. So it does give you a little but more and it's useful in those borderline patients. QRISK3 isn't embedded in GP systems at the moment, so if you want to use QRISK3, you already have to go online to do that. So personally I do go online sometimes and use that already. I think it is a real issue that QRISK2 is going to be removed from GP systems, because it does take extra time, extra steps, it's more coding to do in primary care, so it is a problem. It's being addressed nationally, so we are aware of this and there is work going on try to enable this to continue, but at the moment we don't know the answer to that.

GG: There are new NICE guidelines coming out in May/June. I suspect that we may have even lower thresholds, so at the moment QRISK2 is the right thing to use. 10% is the right thing to use. But people who are 9.5, 9.2, they appear high risk. We know that if they've had high cholesterol for many years, that starting early is important and they're high risk. And young people score much better on the QRISK2 score, and it does seem to be a little bit silly that the age of 30 they score 8.5% and the age of 35 they score 10.1%. I think the new guidelines will basically say that if it's high and they're high risk, start statins slightly earlier. And I think that the advice to all people over 10 definitely, or for a borderline patient, think about QRISK3 or just think about the person in general, because I think that will be the new recommendations in the summer.

Question 5
I was unaware Inclisiran needed to be a fasting LDL >2.6. It isn't specified in the NICE TA or Blueteq that fasting is needed?

GG: I think that to be accurate with LDL, you would have to do a fasting test, so that's a problem with the Blueteq form and maybe the NICE TA. You're not going to get an LDL level unless you do a fasting test and the biochemistry departments are very good at screening out those that are fasting and non-fasting. There are calculators, so sometimes you can't get an LDL when the triglycerides are

very high or for other reasons or if you need to know and you haven't got a fasting test. They're not totally accurate; they give a guide, but certainly for us, for the lipid clinic, it really helps us to have a fasting lipid test. Sometimes we have to re-bleed them if we don't have that data, so if GPs referring can do that for us, that's extremely helpful. I think that unfortunately when we're talking about injectables, we would need a fasting test to decide on those therapies.

Question 6

Is there an opportunity to identify FH through the lung health screening work in Cheshire & Merseyside? It identifies calcification of arteries as part of this work; how could we do it?

SK: Yes, I think there is definitely an opportunity and we did see some of the work presented recently at the CVD Prevention Board. I think there is some work being progressed about how we can look closer at that. I think if you're interested and you live in Cheshire and Merseyside, if you want to get involved in the Lifespan Pathway for Lipids development, I think that is the way to go, because we do need to think creatively, constructively, innovatively about how we're going to pick up FH. I think that most people in the younger age groups or under 40 will not have a lipid profile assessment, so every opportunity we can take to try and pick these up I think is absolutely vital. So if you do want to get involved in the Lifespan Pathway for Lipids development, please contact rosemary.hughes@innovationagenynwc.nhs.uk and we would be happy to support your input.

Question 7

If a patient who attends for their hypertension review tells you that their father has been diagnosed with FH and the patient has a normal cholesterol, do they need a fasting cholesterol test? And do they need anything else?

GG: There would be no need for a fasting cholesterol test, so presumably you know what their cholesterol is, but they definitely need a cholesterol test if you don't know for sure what their cholesterol is. I think that it is important to know whether the father has been diagnosed with a positive genetic test; a positive genetic mutation. If there's a positive genetic mutation, then I think that they should be referred to a lipid clinic for FH screening, cascade testing, to be absolutely sure that they're not carrying the gene. From the data that we (Blackpool Lipid Clinic) have collected, of the 24 patients we cascade tested, the majority had high cholesterol, and of those, three quarters had the gene. So, if you have high cholesterol and you've got the gene which runs in your family, the vast majority are carrying the gene. I think it's about 77% pick up rate. But of our 10 people screened who've got normal cholesterol and they've got the family history and we were expecting none of them to have the gene, one of them had the gene. Their cholesterol was 6.1, so it wasn't dead normal, but it was raised.

So it depends on what this person's normal cholesterol is, but we've certainly picked up with our cascade testing in the last year at least one person with normal range cholesterol who's been cascade testing because their family's got the gene, and they've got the gene. So, if the father is known to have a genetic abnormality, yes, they should be referred for cascade testing. If the father isn't known to have a genetic abnormality, then the father has possible FH, more likely than definite FH, and really the father should probably be referred for genetic testing, because that's the most likely pick up. And if it's positive, then the family should all be screened. If it's negative, I wouldn't do genetic testing for this patient; I would simply keep an eye on their cholesterol.

Question 8

Why do Cheshire and Merseyside use the Welsh Lipid Scale? Are there any advantages?

SK: The Welsh Lipid Score is actually really easy to use, if you've not seen it before. There are pros and cons for the tools for FH testing. The Simon Broome and the Dutch Lipid Network scores almost certainly overestimate the risk of somebody having FH. And I think the FH service initially were worried about being completely overwhelmed in numbers, because they're a very small resource. The Welsh Lipid Score is very accurate in picking up risk of FH, but possibly sifts off some of those patients that are perhaps less likely to have FH. It's also really simple to use. If you've used Simon Broome and the Dutch Lipid Network scores there are some things that make it tricky in primary care to use. So I'd suggest that you have a little look at it. The benefit is that you can actually calculate whether someone should have genetic testing based on their current lipid levels, despite the fact that they're on therapy. So when we are looking in primary care patients who are already treated but might have FH, what we don't want to do is take them off treatment to do a lipid profile. The Welsh Lipid Score enables you to calculate their risk based on their current treatment. So I think it does work really well; it's easy to use, but there are pros and cons to all the calculators.

Question 9

I have been told that if a patient has high cholesterol but also has high triglycerides, it is unlikely to be FH. Would you then offer fibrates?

GG: There are two parts to this question. I think it is less likely to be FH, but it's not definitely not FH, so it still needs to be thought about. And then with respect to therapy, what would you do? Triglycerides can go up for lots of reasons. They're probably much more linked to other conditions and other habits, than cholesterol. Certainly you have lots of badly controlled diabetes patients who have very high triglyceride levels, and when you control diabetes it gets better. Very poor diet, and there are some people who have a terrible diet, that can lead to high triglycerides and improving diet can help. So the first thing to do is take a good history, as to their social habits. Alcohol intake is a third factor which can really affect triglyceride levels, and abnormal thyroid function. So you really need to think, could there be another reason for the high triglycerides and then if you get rid of the high triglycerides and they've just got high cholesterol, it makes it more likely to be FH. There are some very rare genetic abnormalities where there are multiple high lipid profiles, but much less likely.

With respect to therapy, I think the message from today and the message in this patient, is that statins are first line for everything. Because he's got high cholesterol as well as high triglycerides, it can make a small dent in the triglycerides and you can look at the triglycerides from a lifestyle, alcohol, exercise, diet, diabetic control perspective and still start with statins. But if you're getting nowhere, then I think referring to a lipid clinic for help is a very good idea. We do start a lot of people on fibrates, we do add fibrates to statins in certain circumstances, carefully. We do put people just on fibrates, so I think start them on a statin, see where you go, and then if you're not winning then refer to a lipid clinic and in that setting we could safely consider fibrate therapy. We sometimes look at Omega 3, we've mentioned already the new agents as well, that will probably lower triglycerides even though they're not indicated only for triglyceride issues, so there are a few tools that we have available.

Question 10

What are the most common side effects for statins that you have come across in practice? I seem to find that a lot of patients develop constipation and GI issues which put them off continuing with treatment. Any advice or insights?

SK: The commonest statin side effect is the nocebo effect, and this is demonstrated in a range of clinical trials; just two are listed below. The first is a large trial which describe the nocebo effect, the second is a small UK trial that illustrates the problem with nocebo effect. Many trials over the years have researched muscle symptoms, and I find that patients most commonly report muscle side effects (though recently I feel patients seem to be gaining insight that this may be normal aches and pains rather than the statin), but research suggests there is no difference when comparing statins to placebo in this respect. There are rare causes of statin-induced myalgia and it's worth using the NHS Statin Intolerance Pathway to be clear on when to check CK and investigate further. I haven't personally seen much in the way of GI side effects over my years in general practice, but many medications can of course lead to nausea.

https://www.jacc.org/doi/10.1016/j.jacc.2021.07.022#:~:text=Placebo%2Dcontrolled%20trials%20of%20over,of%20thousands)%20provides%20little%20reassurance.

https://www.imperial.ac.uk/news/208436/patients-taking-statins-experience-similar-side/#:~:text=Most%20people%20tolerate%20statins%20but,aches%2C%20fatigue%20or%20joint%20pain.

Question 11

When reviewing historic high cholesterol levels (from many years ago) for assessment for FH, would you request up-to-date fasting lipids, if they have not been checked before?

SK: Yes, it would be preferable to check an up-to-date fasting lipid profile when considering a diagnosis of FH in a patient not already on lipid therapy. If you have a patient already on lipid therapy and want to consider if they should have genetic testing, because their baseline levels may have been consistent with a diagnosis of FH, please always use the age of the patient at the time of the original lipid profile, otherwise the FH risk score will underestimate the need for genetic testing. I mentioned the Welsh Lipid Score today, as this can be used for people on lipid therapy to consider the need for genetic testing. Here is the link: https://fhwalescriteria.co.uk/assistant.html

Question 12

If we can do heel prick tests in babies, is there a simple near patient screening test we could do for adults that could be used more widely, e.g. in community pharmacy or workplaces?

SK: Yes, that is possible, and I personally think would be a great screening option to reach out to people who wouldn't otherwise have their cholesterol checked. The near patient test is an estimate of total cholesterol and is a guide as to whether further assessment is needed, so in the adult population it would need to be followed by a full lipid profile to determine CVD risk or consider a diagnosis of FH.

Question 13
With advancements in statins and where a patient is noted as statin intolerant, do you know of any resources or research that could support a practice member approaching the subject of reassessing that position with a patient?

SK: The NHS Statin Intolerance Pathway is recommended as the main tool to readdress the subject of statin intolerance with patients previously unable to take statins. This provides a simple evidence-based, practical approach to talk to the patient, work through options and determine if it's possible to utilise a statin in people who may previously have had some difficulties. Here is the link: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/08/Statin-intolerance-pathway-January-2022.pdf

Question 14
Should we be checking random or fasting lipid profiles?

SK: In general, we should be using random lipid profiles. The specific indicators for using fasting lipid profiles include:

1. Progressing the diagnosis of suspected FH
2. Checking eligibility for injectable therapies
3. When the random lipid profile shows elevated triglycerides above 4.5, as per NHS Lipid Management Pathway. Here is the link: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/National-Guidance-for-Lipid-Management-Prevention-Dec-2022.pdf
4. When considering treatment with Icosapent ethyl (new add-on therapy for raised triglycerides)

Question 15
Could you tell me more about child parent screening, as I haven't heard about this before?

SK: This is when a baby has a heel prick near patient test at 12 months of age, while attending for baby immunisation. The sample is checked for total cholesterol and if =>5.3 the sample is sent for genetic testing. If this confirms a diagnosis of FH, the whole family is screened. The family receive detailed information on the process at the time of the baby immunisation invite and lifestyle information is provided for the whole family when their baby is screened. Child Parent Screening is already supported by evidence in terms of patient acceptability and effectiveness. Several practices across Cheshire have already started to screen babies. If you are interested in further information, please contact the Innovation Agency: rosemary.hughes@innovationagencynwc.nhs.uk

Question 16
Could you tell me more about how I might identify FH patients and refer to the FH service or secondary care?

SK: Please utilise the NHS Lipid Management Pathway for initial clinical indicators as to whether a person may have FH based on their lipid profile and clinical findings. I think we should always remember to think about possible FH with any baseline lipid profile, and with first acute vascular events, especially if premature vascular disease. A risk calculator or validated clinical criteria should

then be applied to determine the need for genetic testing. These include the Simon Broome criteria, the Dutch Lipid Clinic Network criteria, and the Welsh genetic testing score.

To identify FH patients from a GP population list there are lipid risk stratification tools to run on GP IT systems, which will identify people who look like they may have FH, so further assessment can be considered. Bespoke searches can be undertaken based on the PCN DES FH detection criteria. For more information about available search tools, contact rosemary.hughes@innovationagencynwc.nhs.uk

Referral information for the Cheshire and Mersey FH genetic testing service is contained in the primary care section of the webinar recording and the Blackpool Lipid Clinic in the secondary care section of the webinar recording. For all other areas, referral to a local lipid clinic for further assessment would be the initial pathway to making a genetic diagnosis as not all areas have a specific genetic testing service.

Question 17

I work for a PCN local to Blackpool, and we have identified a large number of patients who have potential FH. Do you have any advice about how we can begin to assess these patients? I don't want to begin referring a large cohort of patients into the lipid clinic unnecessarily.

GG: Firstly, if further clarification may be helpful in support of the response below, please contact rosemary.hughes@innovationagencynwc.nhs.uk and the Innovation Agency will put you in touch with me for more information. The Blackpool Lipid Clinic also offers and Advice and Guidance service. Secondly, for the next six months, the Blackpool lipid clinic has a half-time nurse seconded into the clinic to specifically screen and treat patients for FH, so now would be a good time to make appropriate referrals. We do not yet know if that role will continue after six months.

Thirdly, I would try and triage them into most likely first, if potential numbers are unlikely to be manageable. My suggested order would be:

1. Refer those with a cholesterol off treatment persistently above 9mM (or on high intensity statin total cholesterol persistently >6.5mM) together with a family history of a myocardial infarction in a first degree relative (parent, brother, sister, child) less than the age of 60 or in a second degree relative (grandparent, aunt uncle) less than the age of 50. Exclude those whose high cholesterol may be due to alcoholism, uncontrolled diabetes or uncontrolled thyroid disease until these are under control. If the high level was a one-off or was many years ago, make sure that they still have very high cholesterol levels or have had such levels in the past two years or so.
2. Next, refer those with cholesterol off treatment persistently above 7.5mM but below 9mM or for those on statin therapy an LDL persistently above 5mM on high intensity statin, together with the above family history of myocardial infarction. Exclude those whose high cholesterol may be due to alcoholism, uncontrolled diabetes or uncontrolled thyroid disease until these are under control.
3. Next, refer those with very high cholesterol levels even without a family history, i.e. cholesterol levels off treatment persistently >9mM (or on high intensity statin of >7mM) but exclude those whose high cholesterol may be due to alcoholism, uncontrolled diabetes or uncontrolled thyroid disease until these are under control.

4. Those patients who only have one cholesterol >7.5mM with all others lower than that will be less likely to have FH and might not need referring. Similarly, those with borderline cholesterol levels (7.5-9mM) who do not have a family history of premature myocardial infarction, but rather have a vague family history of angina or unstated heart disease, will be less likely to have FH and might not need referring.

Question 18
How do you test for Xanthelasma/Xanthomata?

GG: Xanthelasma/Xanthomata are not diagnosed by tests; they are recognised on clinical examination, with fatty deposits of a specific appearance found when examining the face, hands, elbows and Achilles tendons. There are photographic examples within the secondary prevention slides of the webinar recording.

Question 19
Continuing with another Xanthelasma/Xanthomata question; If a patient has high total HDL and raised LDL levels, should they be referred?

GG: If a patient has Xanthelasma/Xanthomata and fulfils the LDL criteria for FH then they should be referred to a lipid clinic, whatever their HDL cholesterol is. However, fasting LDL levels would be more helpful than non-fasting total cholesterol levels in these circumstances if HDL levels are very high.

Question 20
I'd like to get support from a clinical pharmacist or nurse to help me look at lipid patients. How might I do that?

SK: There was a recent primary care workforce support opportunity, which invited expressions of interest to apply for workforce support to complete lipid optimisation work at PCN level. 100 PCNs were awarded support, which will commence in 2023. If this intervention is evidenced to demonstrate positive outcomes, it is possible that there may be further tranches of this funding opportunity in the future. For further information about this initiative, or to discuss potential support for lipid optimisation in general, please contact rosemary.hughes@innovationagencynwc.nhs.uk

Question 21
Can you please update us on the situation with the Apo B levels, plus any intervention?

GG: Lp(a) of which Apo B is a substituent does appear to increase risk of cardiovascular events and can now be measured in lipid clinics. The ESC guidelines recommend that everyone should have their Lp(a) levels measured at least once in their lifetime. However, there are no current guidelines (including from the UK) about intervention. There are some trials about to start looking at specific agents that lower Lp(a) levels, to see if they improve outcome. My advice would be that Lp(a) levels, if known, should be treated as another risk factor for cardiovascular disease and if patients are

borderline for starting statin therapy, then having raised Lp(a) levels should push them across the threshold.

Question 22

Which department/hospital do we refer patients with familial hypercholesterolemia to from Lancashire via GP practice? Is there a pathway which has been set up?

GG: There are no current Lancashire-wide pathways, although this is actively being looked into and may change in the future. In Lancashire there are secondary care lipid clinics at Blackpool Victoria Hospital, Morecambe Bay Hospital, Preston and East Lancs; all of which take referrals for FH. Most, if not all of these clinics can consent and refer appropriate patients for genetic testing for FH. The Blackpool Lipid Clinic takes referrals for genetic testing both for proband testing of patients who might have FH as well as cascade testing for family members of patients who have known FH and known genetic mutations. The Blackpool Lipid Clinic also has its own specific Choose and Book option. It will be necessary to contact the other hospitals directly, to find out about their referral options and criteria.