CVD escalation of therapy for secondary prevention scope stakeholder subgroup discussions
Date: Thursday 24 November 2022 Time: 1330-1600

The aim is to improve prevention of CVD, as we are aware that at present many people are not having drug therapy escalated beyond high intensity statins, even after a CVD event.
Factors we need to bear in mind:

- population will remain as per CG181 but focussing on secondary prevention only (note some related TAs have broader populations)
- treatment escalation is likely to mainly be managed in primary care. In this setting, HDL, non-HDL and total cholesterol are the primary measures recorded (as per NICE CG181) due to being from non-fasting samples.

Questions for stakeholder workshop	**Stakeholder discussion points**
Treatment escalation 1. After what time period of trying statins and at what degree of cholesterol control would you consider treatment escalation currently? On what basis? Prompt: How long after 3 months is allowed for further trials to ensure dose optimisation and adherence have been factored in?	**<u>Subgroup 1</u>** Stable levels within a month but you can't see patients within a month. So really it's the next time you can get the patient into clinic, maybe 3-6 months, unless you work closely with primary care. Might get a step up in titration of medication by GPs before they come back to clinic. Is a very broad question, once patient goes onto a statin it's variable what happens. Could go onto 20, 40 and just left on it. Vast majority of GPs don't set a target, lots of ifs and buts within the question itself. Timing? Not before 1month as need time for meds to work, and not later than 6 months as could be at risk of CVD if it's not right. Currently trying to work towards AAC pathway. Trigger to move to next lipid lowering? AAC talks about non-HDL level 2.5 mmol/lt. Need a number to audit against. The current less than 40% target is not helpful. Agree making ref to LDL is problematic, it's a calculated parameter. Take whole history into account, and cholesterol, but not realistic for everyone to do this. Needs to be easy for GPs to put into a pathway.

	Still confusion between non-HDL and LDL, some areas where can't get an LDL reading can only get a non-HDL reading. So catering for both terms would be helpful for some geographic areas. 40% reduction came in because people were to use more potent atorvastatin and rosuvastatin, so the 40% is now unnecessary as have more treatments. Some people will be under treated or missed if don't have the parameters in place. UK is out of sync with the rest of the world. Won't be able to get 100% of patients at the target on statins alone, so need combination therapy. Agree need both figures, non-HDL and LDL. The Samson formula is one of the possible conversion formulas, could be implemented, would be useful, can get the non-HDL and an estimated LDL. But all conversion formulas have limitations and some underestimate in some groups of people. **<u>Subgroup 2</u>** - Patients with high calcium levels might not be considered eligible for secondary prevention - 80mg atorvastatin is the maximally tolerated dose – so we are discussing escalation beyond - What do we mean by secondary prevention? Do patients need to be symptomatic before they can be escalated? - Need to start with lifestyle changes for secondary prevention - Recent European meta-analysis shows that less than half of eligible patients are prescribed and adhere to statins - First, lifestyle changes. Then, statin therapy. What are the targets we should be aiming to achieve?

	- Adherence and tolerance are key – need to investigate different routes of statins for people who are intolerant to one of them - Some evidence suggests that we need to wait at least 3 months post MI to get an accurate lipid profile – but this is disputed - As part of the secondary workup: need to check on smoking, physical activity, and diet. - Maximal level of statins is tricky- might take 1-2 years to bring them up to max dose (3 months at each dose level). So, when do we achieve maximal dosage? - There's a lot of consensus about statins being first line, and adherence to statins being really important, and 40% reduction targets are more based on adherence than around the absolute numerical value. - Do we need to move to an absolute target for escalation? If so, what should that number be? NICE needs to answer this as there isn't consensus around the importance of an absolute target - Is there evidence around which particular cohorts of patients have true statin intolerance and/or adherence issues? Would help clinicians understand who is more likely to be nontolerant - In primary care, it's a pain to do the 40% reduction – another challenge to get the patients in for a review of their non-HDL levels and can be a barrier to escalation for patients who may benefit from it - Some guidance from NICE to clinicians around evaluating residual risk aside from LDL-C would be helpful - It's difficult to drive down someone's LDL-C under 1.8 without PCSK-9 inhibitor: but currently these therapies are only reimbursed for very high LDL patients - There is a lot of confusion around statin intolerance

	- An absolute target is something that can facilitate good clinical care because the 40% reduction is more difficult to use - Some confusion around non-HDL and LDL: non-HDL may not always be included in the lab work-up, clinicians may need support in understanding when to request and how to interpret - 1st line of treatment with high CVD risk should be low dose statin in combination with ezetimibe [NOT high dose statin] – this would also optimally treat the 1/3 of people who have high cholesterol absorption - If we keep changing the targets it does a huge amount to reduce the confidence that patients have in their clinicians, and increases the demand on the healthcare system that is already stretched - Most people will prefer an absolute value – but a percentage reduction may be more accurate - Calculation of LDL-C based on lab test is not accurate people with high triglycerides (>4.5) - Laboratories produce different reports depending on where in the country you are – would be useful if there were consistency in the results - Need some homogenisation of what testing should be done: need guidance on fasting/non-fasting, need consistency in outputs, need outputs that can inform physicians on what action is needed for the patient - Tolerability may be better from a lower-dose combination of two drugs (statin + ezetimibe) - In Wales, tests are standardised, we get LDLC reported on fasting and non-fasting samples

	- Suggest a follow-up at 2 months instead of 3 months – check in on patients while they are still in cardiac rehab so that action can be taken by cardiac rehab team if relevant - Are we prioritising population health or individual health? - If the target is too low, people may ignore it as it becomes too difficult to achieve **<u>Subgroup 3</u>** The group acknowledged the delays in provision of care and prescribing services experienced in this area by people with CVD. It was noted that it would generally take 10 – 12 weeks just to get a blood test in the NHS in contrast to service provision in the private sector which would take about 4 weeks. The group agreed that ideally, within 2 weeks people with CVD should have access to lipids test results, and any required changes in care should be escalated at 6 weeks. The group noted that the time periods applied would differ for discrete group of people, particularly: • People who have had an event and are on high intensity statin (escalate or reduce within 3 months) • People who have heart disease but have not had a key event. (Managed within 4 – 6 months before deciding to escalate) Stakeholders noted the significant primary care resource impact to deliver improved services in terms of both review and escalation. The group was aware of the uncertainty around delivering consistent care in this area. They thought it hard to transfer direct evidence to care in the use of LDL and went on to say that measuring non-HDL would be the best route, and also incorporates LDL. The group agreed that the 40% reduction target is not well used, partly because of a lack of baseline lipid measurements They acknowledged the challenges of getting people prescribed the new lipid drugs and were keen to make it simple for clinicians to access. One example was

	that PCSK9i TAs use LDL-C levels as part of the eligibility criteria which causes access delays.
2. Is ezetimibe coadministration the accepted next step after high dose statins (assuming no intolerance), or are the injectable treatments (inclisiran, alirocumab, evolocumab) also considered at this stage? Is it standard practice to offer ezetimibe if statins are contraindicated or not tolerated?	**<u>Subgroup 1</u>** Language must change towards achieving risk reduction by lowering LDL by as much as possible that the current HTA allows. Ezetimibe will be a good option Ezetimibe use across the country is very low 3%. Why? Are people moving towards the injectables over ezetimibe? It's because ezetimibe didn't have outcome data. Mainly secondary care use it. Should open with a high intensity statin and ezetimibe. Not had a target since 2008 in UK, but other countries have had a target. If using best evidence people will talk about 1.4 mmol/l LDL. Different drugs have different targets. What evidence has been used to inform the 1.4 target? RCTs. FDA and EMA require the trials on top of a statin; combination therapy. You could reduce event rates with combination therapy, like hypertension colleagues. Could have one standardised level for all drugs, then put the drugs in an order based on efficacy and cost-efficacy. Confusing barrier to have all the different thresholds. Can we do this? Would support it if we could. We could do sequencing of the TAs, but might contradict the thresholds they set. So not straightforward and there have been commercial agreements based on the TAs. **<u>Subgroup 2</u>** What do we do when we escalate? Is there uncertainty on who to treat with ezetimibe or which drugs to use when escalating therapy? - 20% of people who've had a CVD event aren't on a statin – clinical knowledge is needed in this space

	- 10% of eligible patients are on ezetimibe: there is a lack of awareness that this is an appropriate next line therapy and high threshold for eligibility (going through high-intensity statins) - True intolerance vs patients declining statins: far more patients reject statin therapy than are truly intolerant of it - At what point does patient choice become a factor? How much weight should we give to patient voice? - Guideline should also support clinicians in overcoming patient nonadherence/rejection of statins - Importance of patient decision aid around starting statins - What do we do about patient refusal? It takes clinical time to explain to someone what potentially having a stroke means [disability, impact on family, etc]. There is some evidence that involving the family in decision-making can be beneficial. NICE should look into interventions to improve adherence - In oncology, we had the 'PREDICT' tool which was useful in explaining to patients the benefits of chemotherapy. In CVD medicine, we don't have a good way of explaining to patients the benefits of therapy - In order to prescribe the patient with an escalation treatment, if the evidence, risks and benefits are the same, clinicians will probably go for the cheapest option on the advice of their pharmaceutical advisor - We are talking about secondary prevention as though it is a homogeneous group: is there an evidence base for different degrees of risk [e.g. 2 vessel disease vs 1 vessel]? **<u>Subgroup 3</u>**

	The group noted the lack of evidence in this area and thought it important to provide a clear pathway as there is a lot of uncertainty around which agent to offer. It was noted by one participant that the National Lipid algorithm has put all of these therapies into the same box (ezetimibe and injectable treatments), without providing guidance on which to choose in what circumstances. The group acknowledged that the guidance currently used support GPs in prescribing: usually this recommends starting with a high dose statin and then moving to ezetimibe if needed (with an LDL-C target of <1.8 as the aim). PCSK9i thought to be appropriate, but the group was aware of evidence of intolerance in people who have used these drugs. The group was aware that GPs have advised that they will specifically not use inclisiran until more evidence is available, including CV event outcome data. The group also noted that everything else is more easily accessible. The group mentioned that ideally, prescribing is done in partnership with doctors and people living with CVD. They stressed the importance of the risks, benefits, and any uncertainties being presented to patients. This would support informed decision making. It was thought that efforts in this area would be greatly supported by a decision aid tool. The group noted that clinicians often use atorvastatin 40 mg in combination with ezetimibe (as opposed to the recommended 80 mg of atorvastatin), owing to the perceived small lipid-lowering benefit compared to the increase in adverse events for the higher dose of statin.
3. Is there uncertainty about when, or to whom; a. Ezetimibe* should be given in addition to a statin,	**<u>Subgroup 1</u>** AAC guidance is clear on this just not been applied very well in a systematic way. Bempedoic as a monotherapy will achieve 28% LDL lowering. Adding in ezetimibe will achieve higher lipid lowering. Monoclonals are only initiated in secondary care. Bit hit and miss, not systematic. It could change, but currently it's specialist clinics who give monoclonals, but they are self injected so it could be done in primary care.

b. Bempedoic acid** should be given in addition to ezetimibe in people in whom statins are contraindicated or not tolerated? Notes:*TA recommendation states that ezetimibe can be coadministered with a statin when serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy. Appropriate control of cholesterol concentrations should be based on individual risk assessment according to national guidance on managing cardiovascular disease in the relevant populations. [NB CG 181 does not recommend risk assessment for secondary prevention] ** It appears unclear as to how 'LDL c control is defined (2nd bullet below). Bempedoic acid with ezetimibe is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-	If the drug is safe to use in primary care it should be used in primary care, self-administered, need to get away from these confidential agreements with the drug companies. Cost differential – not using a monoclonal antibody in patients who are eligible for inclisiran. Few other considerations too in the decision making process. One of the differences is that inclisiran is available in primary care, and people don't need to be referred to secondary care. Dosing frequency is also a consideration between treatment options. Changing and adjusting the thresholds to be able to be discharged back to primary care. Not sustainable to keep everyone in secondary care. Novartis are not going to give inclisiran to the NHS at huge discounted cost forever. **Subgroup 2** Due to a lack of time this question was not discussed. **Subgroup 3** A. • Yes. Particularly for groups where they have had a second event, unless the patient is able to take inclisiran. • Nonadherence around patient use was noted, due to the side effects (erectile dysfunction, bloating, tiredness, nausea, abdominal pain). • The group thought however, that side effects, and the effectiveness of these drugs are largely predictable and discussions to this effect should be held with patients. They also thought it would be helpful if follow up could be carried out by a non-clinician/pharmacist. Reducing the need to for clinician/medic follow ups would significantly reduce resource need in this area.

familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if: • statins are contraindicated or not tolerated • ezetimibe alone does not control low-density lipoprotein cholesterol well enough and • the company provides bempedoic acid and bempedoic acid with ezetimibe according to the commercial arrangement.	• It was thought that the current TA on this area does not provide clinicians with clear advice, as the targets mentioned are considered debatable. B. • Bempedoic acid use thought to be very low and evidence weak.
4. If other options are alternative 2nd line options, is it clear when you would give one of these rather than ezetimibe? Prompt: Can the decision be based on the TA recommendation criteria for eligibility for those drugs (see below), and if the person doesn't meet those they have ezetimibe? **Inclisiran** - if fasting LDL-C ≥ 2.6mmol/L despite maximum tolerated lipid lowering therapy (TA733)	**<u>Subgroup 1</u>** Moot point. Only group where you would sequence is if your LDL is 3.5 or 4. When does it publish? 2026. Orion 4 and Victorian 2p 2027. Some people are genuinely intolerant to statins so have bempedoic acid, monoclonal antibodies etc. Glaring hole that can't give patients effective treatment who fall between the cracks. By keeping a patient on a particular drug you could push them outside the eligibility of achieving their lowest LDL. The people who will be disenfranchised are the people below 2.6.

PCSK9i: NICE TA393 Alirocumab & NICE TA394 Evolocumab Primary non-FH or mixed dyslipidaemia (with CVD) High risk 1: LDL C > 4.0 mmoL/L, Very high risk 2: LDL C > 3.5 mmoL/L CVD defined as: History of any of the following: 1. ACS; coronary or other arterial revascularisation procedures; CHD, ischaemic stroke; PAD. 2. Recurrent CV events or CV events in more than 1 vascular bed (that is, polyvascular disease).	**Subgroup 2** Due to a lack of time this question was not discussed. **Subgroup 3** During this discussion the group mentioned the difficulties involved in prescribing PCSK9i. Patients would only have access after a lengthy wait and challenges experienced, navigating the service. It was thought that it was very easy to provide clear guidance on the use of PCSK9i. The service is currently offering what primary care is comfortable using. Once referred to a lipid clinic, it is at that point that novel agents would be considered. The group noted concerns that people who are at high risk could find themselves on a long waiting list. They though it important to consider interim measures, such as use of ezetimibe, that could be applied while the patient waits to be seen by a clinic. The group saw one of the biggest issues as the fact that PCSK9i requires specialist referral, for patient access, but were aware that once robust outcome data for inclisiran becomes available this issue will resolve. Agents could potentially become accessible; it would escalate the pathway to meet patient needs in a timelier manner. It's hoped that actual self-administration by the patient would be eventually possible, but the service is not yet at that point, despite there being some noted progress in discrete regions, where they have also noted the effectiveness of the drug.
5. Is there uncertainty about what order to give these treatments? Is this a priority issue? If yes, should drugs with CV outcome data should be used in preference to those with only lipid lowering data, irrespective of potential effectiveness/cost effectiveness based estimates from LDL lowering?	**Subgroup 1** Due to a lack of time this question was not discussed. **Subgroup 2** Due to a lack of time this question was not discussed. **Subgroup 3** It was thought that pathways and processes get in the way of prescribing and the order of treatment options is more based on practicalities of service delivery rather than evidence. The group agreed that drugs with CV outcome data should be preferred.

	The Orion 10 and 11 trials were mentioned, and it was noted that these do provide some provisional outcome data for inclisiran. The group was aware of that and the positive results. They did note, however, that Orion 4 was scheduled to take another 3 years. The Clear-Outcomes trial was also mentioned. The group was aware that this trial, which is evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance. Discussions turned to inclisiran once again, and the group noted known safety issues in relation to its use.
6. If yes to the above, is there uncertainty about when to escalate between these (a threshold for each escalation), or does the TA criteria inform this after a certain period of review?	**Subgroup 1** Due to a lack of time this question was not discussed. **Subgroup 2** Due to a lack of time this question was not discussed. **Subgroup 3** There is uncertainty about when to escalate between the drugs mentioned above.
Treatment target 7. Is the question of what target treatment should aim for important? What evidence should inform this?	**Subgroup 1** Yes need a target definitely. Is difficult to give patient additional treatment so it's useful to have a target in order to explain the need for more treatment. Simplicity of when to give inclisiran. AAC guidance is great but busy clinicians don't have time to read it. JBS3/JBS4 – be good to have an aligned target. Have one message that would be good. Need clear definition of CVD as some people with CVD are asymptomatic so is useful to have a target.

	Need another target for familial hypercholesterolaemia and primary prevention. Would want to be consistent across the world. **<u>Subgroup 2</u>** What targets should we be aiming for? - With a 40% reduction target: It may be difficult for patients to know if they have achieved the target, especially if they change practice. An absolute target is easier to orient practice around. - Need NICE to look at the primary evidence base - Don't set a target that's unachievable. Consider different contracting models: setting a different target for reimbursement compared to a target for primary care/clinical practice - Look at mean cholesterol levels in UK population: consider that non-HDL levels on average are 4 mmol/L; so a 40% reduction from there is about 2.4 - The current NICE CVD suite committee has mentioned that there is no lower base limit for LDL - Is there a lower level for harms? - If we orient our secondary prevention around a 40% reduction or an absolute number of 2.4, we ignore things like benefits of ACE-inhibitors, treating tobacco dependency, other interventions that reduce the risk of CVD events but don't impact the LDL level - Patient with a much higher starting LDL (6 vs 3) is going to have a much higher residual CVD risk - Don't forget other lipids – not just LDL-C

	- Consistency with European guidelines that a lot of clinicians refer to: if NICE comes up with something that is different, there could be a lot of paradoxes - Usually NICE guidance leads the way so if NICE disagrees with EU guidance, that will trump the other guidance - In NICE's literature review, it would be good to know if there is any evidence for populations that suffer worse outcomes **Subgroup 3** • The group thought that after treatment targets are important. • They were aware of the European guidelines but noted that that guidance does not consider health economic priorities. • The group noted that patients who are already on statins, or who have had an event, would be on a different pathway. They also noted that within the secondary prevention population there is a range of risk levels still, however those who have been non-adherent should be considered separately and may have different targets. • It was also thought that what target to use could be looked at in terms of which event the individual is experiencing (first, second, third). • The group considered that cost-effectiveness modelling could inform the threshold.
8. Do you agree that there is not a lower limit of LDL lowering in terms of leading to harms? If setting an absolute target, would you stop escalating treatment once that target had been achieved?	**Subgroup 1** Due to a lack of time this question was not discussed. **Subgroup 2** Due to a lack of time this question was not discussed. **Subgroup 3** • The group mentioned that the side effects of the drugs that will be experienced by patients when trying to achieve lower limits of LDL would be a deterring factor in terms of adherence (although there is no lower limit of LDL-C that was cause harm in itself). So, although lower limits

Prompt: If there are cost effective treatments that have not yet been tried when this target is reached, is it appropriate to stop treatment once a agreed target is reached?	generally thought to be better – this would be achieved at a high cost to patients because of side effects. • The group agreed that injectables would address the non-adherence component, as opposed to adherence issues with orals. • Practical benefit of having a lower target and clinically they agreed that treatment would not be escalated once the patient's target is achieved. Once the target is met, physiological interventions would be considered at that point– which are thought to work when there has been a significant lifestyle change. • Other considerations which add a layer of complexity include the cost of the therapy and using target levels alongside other combination therapies. • It was also discussed that if LDL-C targets were achieved treatment could be de-escalated. • One member described the tension between setting a threshold for escalation and an absolute target, which could be incompatible.
General 9. What would your top 3 priority areas be?	**<u>Subgroup 1</u>** Starting with combination therapy Early escalation of therapy for injectables Recognition that a lot of people are coming back in secondary care. Set a target Use combination therapy Get it into QOF. Set the target 2.5 HDL 1.8 non-HDL Have the conversation around risk reduction. To help with sequencing of therapies. Set a target Make it simple

	Having a QOF target of less than whatever, for GPs to have an incentive to do it/prioritise it. **<u>Subgroup 2</u>** What are the key priorities for this piece of work? - Testing – need clear, homogeneous guidance on how to test and what to test - Embed guidance with clinicians in practice - Answer the question of the benefits of an absolute target and what that target should be - Don't lose sight of primary prevention - Oral therapy (not injectable that they need to travel for), cheapest outcome that we have outcome data that it will work **<u>Subgroup 3</u>** • Clarification needed on who can and can't start specific therapies. • Ease of restrictions to stop waiting lists being created. Improving access for more life-threatening conditions. • The need for standardised referral forms for lipids clinic. Uncomplicated, clear documentation that provides steps in the referral notes, ensuring that interim measures are clear. This will support triaging referrals, and ensure that its noted, what treatments and interventions have been tried. • Guidance needed on the use of fasting/ non fasting samples for triglycerides measurement. • Building Information and support into service delivery so that patients understand various dosing options. Version of treatment/efficacy/route. • Ezetimibe guidance to be improved as currently considered unclear.

10. Are there other key issues in secondary prevention escalation of treatment that you think it's important for the guideline to address?	**Subgroup 1** Very important to have an eye on the future, need to know what treatments are coming up. There are a number of therapies coming along that need triglycerides and LDL. Be broad and not being hung up on LDL non-HDL readings. Have a broad brush approach. **Subgroup 2** - Choose the simplest route for clinicians - I believe in targets, I think they are the right way to go. Don't hedge bets, be clear and concise and practical even if the evidence is unclear - Hard target is better - People will refer to multiple guidelines so ensure they are aligned. **Subgroup 3** • Creating ways in which patients could initiate access to their own tests without having to wait for specialist access and avoid long waiting times. • Providing clarity in Primary Care about when tests should be done post-event and improving access to testing in primary care. • Understanding what additional/more aggressive care is required if comorbidities exist. • Facilitating a structured medication review for those requiring secondary prevention with someone who has the time to undertake a thorough review • Including pharmacists in lipid optimisation to help resource issues and reduce delays to accessing lipid specialists.

11. How should polypharmacy risks be taken into account?	**Subgroup 1** Due to a lack of time this question was not discussed. **Subgroup 2** - Polypharmacy is always an issue especially for older patients. If there is any evidence - Guidelines only include when to start a drug – would be useful if they also said when to stop Be clear about the sequence of therapies to add (e.g. if you are not meeting target X at time point Y, take step Z…) and need to communicate to patients (via decision aid). **Subgroup 3** • Group thought UK has always been behind in terms of polypharmacy, due to hesitancy to manage the identification of multiple side effects and adopt combined pills. • More information now available on fixed dose combinations, but the UK has some way to go. • It was noted that triple therapy in a single pill is not yet available in the UK but is being used internationally. • The group considered this to be a risk/benefit issue, and remain keen to prevent a CVD event, and polypharmacy could assist.
12. Are there any published references or trials due to report soon you are aware of that could inform the key issues discussed?	**Subgroup 1** Due to a lack of time this question was not discussed. **Subgroup 2** Due to a lack of time this question was not discussed. **Subgroup 3** • Clear Outcomes trial

	• PCCS Compass trial was mentioned. • FOURIER long-term follow-up • Consideration of observational and real-world data.