Cardiovascular disease: risk assessment and reduction, including lipid modification - Escalation of Therapy

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AHSN Network	Guideline	General	General	**Education materials** The Health Innovation Networks led the delivery of the national lipids programme over 3 years. The inclisiran workstream remains live. The proposed content of the consultation would lead us to consider re-framing the messages we have worked hard to deliver to our clinical colleagues. A national education programme in partnership with HEART UK and a multitude of locally developed education and toolkits have aligned to NICE, the AAC guidance, the AHSN pathways, JBS3, QOF, the National Clinical Guideline for Stroke and ACA ACC. It would be extremely unwelcome disruption, resource heavy and wasteful if we were required to update these materials.	Thank you for your comment. The committee recognise that materials including educational may have to be updated if they wish to incorporate the recommendations made in the guideline and appreciate the work involved in this. However, these recommendations are based on the clinically and cost effectiveness to ensure the optimal allocation of resources for the NHS. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. NICE's implementation support team are planning to work with partners (including the HINs) to support the update of materials if requested.
AHSN Network	Guideline	General	General	**Sequencing of Therapy** Whilst we appreciate your document is not intended as a clinical pathway there is a risk that it may be misinterpreted as such by some particularly with reference to the sequencing of ezetemibe. It is clear that for the majority of high-risk patients, a combination lipid lowering therapy will be required to achieve treatment goals. It is our view that following maximally tolerated statin therapy further treatment escalations should be a shared decision between patients and their clinicians. We would urge caution in language and presentation that could create the	Thank you for your comment. The recommendations have been edited to make it clear that all of the relevant lipid lowering treatments should be considered, in people above the target, in accordance with the NICE technology appraisals (see 1.7.10). The committee have made a new recommendation 1.7.8 recommending that there should be a discussion between the clinician and the person when deciding whether to escalate treatment.

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				impression all patients should receive a statin and ezetemibe before consideration of additional therapy. We believe this would be prejudicial to the optimal care of many patients and needlessly increase clinical contacts prolonging the time taken to achieve target levels. In our view you need to be more explicit in this point relating to the sequencing of statin, ezetimibe and other therapy.	
AHSN Network	Guideline	General	General	**Harmonisation of treatment targets and guidelines** Further clarity on statin intolerance would also be welcome. We receive feedback that 80mg of atorvostatin is often not well tolerated, leading to drop out from primary care and cardiac rehab. Always starting on this intensity leads to additional appointments and prolongs the time at cardiovascular risk until a maximally tolerated dose is up-titrated. We would welcome a clearer recommendation of the alternatives. There is also some confusion on the use of bempedoic acid as a single agent or in combination with ezetimibe and what the proposed changes are recommending.	Thank you for your comment. Recommendation 1.7.3 covers when to start on a lower dose than atorvastatin 80mg. Recommendation 1.10.2 now refers to the NICE technology appraisals on the lipid lowering treatments. TA694 recommends that bempedoic acid should be offered with ezetimibe.
AHSN Network	Guideline	General	General	**Harmonisation of treatment targets and guidelines** We welcome the departure of the 40% reduction aim from earlier guidelines. We believe your review represents an opportunity to harmonise guidelines across NICE, the Quality and Outcomes Framework and the European Society of Cardiology. In our experience coordinated messaging achieves greater impact and penetration amongst prescribing clinicians and avoids criticism of generating competing or confusing guidance. We	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions

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				recommend that a target of 2.5 mmol/l is adopted in your guidance in order to achieve this clear message, rather than changing to 2.6 mmol/l which would be a minimal but confusing change. Should you choose to pursue LDL as the favoured assay (see above) we recommend that the threshold is lowered to 1.8 mmol/l to avoid conflicting messaging into the system. A further debate on absolute thresholds is unhelpful and potentially distracting when clinical efforts would be better focused on identification and treatment of eligible patients.	of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. NICE's implementation support and communications colleagues are working with external partners (including HIN) to consider targeted and clear comms for this update and to support harmonisation of support materials and activities
AHSN Network	Guideline	General	General	**Use of LDL versus Non HDL in measuring cholesterol** The availability of LDL testing is patchy across the country and access to LDL results has been raised as a barrier to the introduction of new therapeutics or pathways with us on multiple occasions. Furthermore, a move to fasting tests for LDL would swamp phlebotomy services across the UK and make this unmanageable if large volumes of our at risk population need a blood test first thing in the morning. The majority of cardiovascular risk assessment and reduction will be undertaken in primary care settings. It makes no sense to introduce a guideline which relies on a test which cannot be obtained in large areas of the country. We recommend that non-HDL, reported by all NHS laboratories, is a more pragmatic marker for risk assessment and should be used in favour of LDL. At the very least an non-HDL equivalent should be included in	Thank you for your comment. The committee recognised that LDL testing varies and could be a barrier to implementation. A non-HDL value is therefore also given in recommendation 1.7.1.

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				the guideline for those practitioners unable to access LDL assays from their local laboratory.	
Amarin UK Ltd	Guideline	006	026	1.6.9 Section on Escalating treatment for people on statins – only includes ezetimibe, alirocumab, evolocumab and inclisiran. However there are other therapies that can be added to statins for eligible patients such as Icosapent ethyl. The recommendation to include Icosapent ethyl is based on: • NICE stated there are currently no treatment options for these patients with moderately elevated TG and they concluded that people with elevated triglycerides who are have statins with or without ezetimibe would welcome a treatment option, hence Icosapent ethyl should be added as an option in line with its TA805 • The Committee for Human Medicinal Products of the EMA concluded that *"….**icosapent ethyl is considered to be a new active substance** as it differs significantly in properties with regard to efficacy from EPA and mixtures of constituents contained in medicinal product(s) previously authorised within the European Union ("omega-3-acid ethyl esters 90")* • In REDUCE-IT, treatment with icosapent ethyl 4 g/d versus placebo, in patients with elevated TGs,	Thank you for your comment. These recommendations form part of the guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification. That guideline includes recommendations on omega 3 fatty acid compounds, and on combination therapy (1.12.5 – 1.12.7) which include reference to icosapent ethyl in line with NICE TA805."

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				on background statin therapy with median LDL-C 1.9 mmol/L, resulted in: • 25% Relative reduction in first 5-point MACE events (4.8% ARR, NNT 21) • 26% Relative reduction in first 3-point MACE events (3.6% ARR, NNT 28) • 30% Relative reduction in total 5-point MACE events • 20% Relative reduction in CV death (0.9% ARR) • 31% Relative reduction in fatal or non-fatal MI (2.6% ARR) • 28% Relative reduction in fatal or non-fatal stroke (0.9% ARR) • 30% Relative reduction in total (first and subsequent) ischemic events for the primary composite endpoint • 1% Absolute increase in adjudicated atrial fibrillation or flutter requiring hospitalisation for at least 24 hours • 1.9% Absolute increase in any bleeding-related adverse events, but no increase in bleeding-related serious adverse events	
Amarin UK Ltd	Guideline	007	020	1.6.14 – Measure liver transaminase, total cholesterol, HDL cholesterol and triglyceride levels and calculate non-HDL cholesterol and LDL cholesterol about 3 months after starting or changing lipid-lowering 23 treatment	Thank you for your comment. Recommendation 1.11.1 has been edited and now recommends a full lipid profile which could be non-fasted or fasted.

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				Suggestion to change to either fasted lipid tests throughout or follow the ACC guideline (2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia) where they provide both fasted and unfasted values to use before considering the addition of triglyceride risk-based nonstatin therapies: • Secondary prevention patients with clinical ASCVD and fasting triglycerides ≥150 mg/dL, or non fasting triglycerides ≥175 mg/dL and triglycerides ≤500 mg/dL.	
Amarin UK Ltd	Guideline	007	024	1.6.15 - Consider an annual non-fasting blood test for non-HDL cholesterol to inform the discussion. The recommendation for only non- HDL-C annually does not cover all the atherosclerotic risk factors. A full lipid profile is important in ASCVD assessment, including triglycerides, LDL-C. To align with other recommendations such as ESC, in which the section on 'Recommendations for measuring lipids and lipoproteins to estimate risk of atherosclerotic cardiovascular disease' includes TC, HDL-C, LDL-C, TG and non HDL-C. Also the NICE AAC pathway which recommends 'Measure non-fasting ***full lipid profile*** (total cholesterol, HDL-C, non-HDL-C, triglycerides) and HbA1c'.' The recommendation to include all lipid parameters including TG is based on:	Thank you for your comment. We have added full lipid profile to recommendation 1.11.1 It is expected that if LDL needs to be calculated this will be performed by the laboratory using the appropriate equation.

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				• Epidemiological clinical, and genetic studies which have shown that elevated levels of TGs are an independent marker of CV risk • NHS England estimated that between 25% and 35% of people having statin therapy have elevated triglycerides. The patient and clinical experts explained there is an unmet need for this population. • International guidelines recognise that CV risk is increased with TGs over 1.7 mmol/L • numerous studies in patients on statin therapy with controlled LDL-C levels, but with moderately elevated TG levels have been shown to be correlated with elevated residual risk for CV events such as angina, MI and stroke. • The risk of events is probably due to the combination of several factors, including lipoprotein unbalance, inflammatory risk and pro-thrombotic status that account for high incidence of new CV events. There is a strong correlation between elevated TGs and residual CV risk, thus facilitating the identification of high-risk patients. To ensure all aspects of the lipid profile can be calculated accurately the updated ACC pathway also comments on the management of LDL calculation when TG>4.5mmol/L in which the alternative equation (eg Sampson, doi:	

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				10.1001/jamacardio.2020.0013) or beta-quantification could be used.	
Amgen Ltd	Guideline	005	005	**Rec 1.6.1** Amgen welcomes the inclusion of a target for the treatment of high cholesterol, giving clinicians clarity over how their patients should be managed. NICE's own analysis showed that LDL (low-density lipoprotein) is more closely linked to major cardiovascular events than non-HDL (high-density lipoprotein) cholesterol. Amgen recommends that this could be better represented in the guidance by stating a preference for LDL testing. Testing is becoming more widely available, and cheaper, through the development of technologies such as point of care testing. Considering this, we believe that the guideline will be future proofed if a preference is indicated for LDL testing. Local constraints around capacity or cost for testing may still take precedence in determining which type of test may be offered, however Amgen maintains that clinical evidence should be prioritised in the management of these high-risk populations. Therefore Amgen asserts that "…non-HDL cholesterol levels…, or where non-HDL is not recorded, LDL cholesterol levels" should be replaced by "…LDL cholesterol levels…, or where LDL is not recorded, non-HDL cholesterol levels".	Thank you for your comment. Recommendation 1.7.1 has been edited.. The trial evidence for LDL was the more robust both in terms of cholesterol reduction for each treatment and the relationship between cholesterol reduction and CVD outcomes. This evidence determined the most cost-effective target in the economic model (see the committee's discussion of the evidence in evidence review D). However, non-HDL is also given in the recommendation..

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Amgen Ltd	Guideline	005	007	Internationally, 1.8mmol/l (1.4mmol/l for very high-risk patients) is widely accepted to be the target for optimising lipid management. Retaining a 2.0mmol/l would make NICE an outlier in the pursuit of better care for people with high cholesterol.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence.
Amgen Ltd	Guideline	005	007	**Rec 1.6.1** Amgen believes that inconsistency with other guidance may impact on the ability to implement guidance. The risk is that confusion will be perpetuated within clinical practice as to how cholesterol should be managed. Specialists working within lipid management are familiar with the 1.8mmo/l target and it is Amgen's experience that these specialists seek to treat aggressively to try and reach this, in line with AAC (Accelerated Access Collaborative), JBS3 (Joint British Societies for the prevention of cardiovascular disease) and ESC (European Society of Cardiology). Such specialists are likely to continue to treat to 1.8mmol/l regardless of the CG181 guidance in the clinical interest of their patients, thereby	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. Cost effectiveness has not been considered by other guidelines. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England

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				negating any anticipated cost benefit of recommending a higher target at 2.0mmol/l. Within primary care the existing QoF (https://www.england.nhs.uk/wp-content/uploads/2023/03/PRN00289-quality-and-outcomes-framework-guidance-for-2023-24.pdf) indicator has established 1.8mmol/l as the target for LDL management, consistent with AAC, JBS3 and ESC guidelines. Amgen does acknowledge the creation of a new indicator intended for introduction to QoF however this will not take place until April 2024 at the earliest, meaning an overlap of three months during which QoF will still incentivise 1.8mmol/l against CG181's target of 2.0mmol/l. There is a risk that GPs will continue to work to 1.8mmol/l even beyond April, again negating any cost benefit. The recommendation of a 2.0mmol/l LDL target is thus likely to prevent smooth implementation of CG181 within both primary care and specialist care. A target of 1.8mmol/l in this guideline would lead to a greater chance of success in achieving consistency and lack of variation in clinical practice nationally.	to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. Recommendation 1.7.11 recommends that ezetimibe can be considered to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is achieved.
Amgen Ltd	Guideline	005	007	**Rec 1.6.1** The European Society of Cardiology (ESC) *Guidelines for the management of dyslipidaemias* (https://academic.oup.com/eurheartj/article/41/1/111/5556353?login=false#207091838) goes further than AAC and	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. Cost effectiveness has not been considered by other guidelines. The cost per

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				JBS3 guidance to suggest that a target of 1.4mmol/l should be sought in very high-risk patients. This is reinforced in the AHSN Network's *Lipid Optimisation Pathway* which states that "Following ACS a lower LDL-C target < 1.4 mmol/l may be appropriate " (https://www.ahsnnetwork.com/wp-content/uploads/2023/03/Lipid-Optimisation-Clinical-Pathways-Acute-v544.pdf). This is another instance of inconsistency between the proposed guideline and other work the NHS has done to improve lipid management. The distinction between high and very high-risk patients is lacking within this draft guideline. Amgen believes that in order to optimise care for people with high cholesterol it is important that the body of clinical evidence and guidelines should be prioritised above the cost effectiveness analysis when it comes to determining treatment targets. We strongly recommend there should be a provision within this guideline for a lower target of 1.4mmol/l for very high-risk patients.	QALY of a target of 1.8 (used in the QoF) compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C (or lower) would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. Recommendation 1.7.11 recommends that ezetimibe can be considered to reduce CVD risk further, for example very high risk patients, even if the lipid target for secondary prevention of CVD is achieved. The target is based on both clinical and cost effectiveness. The RCT outcomes on treatment efficacy was used to inform the economic model.
Amgen Ltd	Guideline	005	007	**Rec 1.6.1** Amgen has reviewed the cost effectiveness analysis that informs the recommendation of a target at 2.0mmol/litre and concludes that, while this in itself is robust, it does not reflect optimal care for secondary prevention patients.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. Cost effectiveness has not been considered by other guidelines. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C

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				Amgen believes that CG181 should strive to deliver the level of care at which risk of major cardiovascular events is minimised as far as possible, in order to avoid harm to patients and subsequent costs to health & care systems from managing acute illness. There is evidence to show that every 1mmol/l LDL reduction reduces cardiovascular risk by 20-25% (https://www.acc.org/Latest-in-Cardiology/Articles/2018/02/16/09/31/How-Low-Should-We-Decrease-LDL-Cholesterol-in-a-Cost-Effective-Manner), suggesting that lower targets should be sought to optimise care in this secondary prevention population. NHS England's Accelerated Access Collaborative (AAC) *Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD* (https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-v6.pdf) and Joint British Societies for the prevention of cardiovascular disease (JBS3) (http://www.jbs3risk.com/pages/6.htm) both recommend target values of 1.8mmol/litre LDL (2.5mmol/l non-HDL). These recommendations have been developed over time to deliver a clinically driven consensus on optimal treatment levels. As such Amgen expects that the treatment target within 1.6.1 to be reduced to 2.5mmol/l non-HDL or 1.8mmol/l LDL.	mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. Recommendation 1.7.11 recommends that ezetimibe can be considered to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is achieved.

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Amgen Ltd	Guideline	007	007	**Rec 1.6.11** Amgen believes that the recommendation to maintain ezetimibe alongside the maximum tolerated intensity and dose of statin supports our view that the treatment target should be lowered to 1.8mmol/l. This recommendation directs readers to continue lipid lowering therapies once the 2.0mmol/l has been reached. This can be read as acceptance that the 2.0mmol/l level is not sufficient and that patients should continue to be treated. In this instance, Amgen asserts that a 1.8mmol/l target is consistent as it again drives a more ambitious treatment regimen, thereby more likely to reduce lipid levels to lower risk levels.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. We have edited recommendation 1.7.11 to make it clear that ezetimibe should be considered to reduce CVD risk further. This would depend on several factors and would be discussed as part of shared decision making with the person. The recommendation is aimed at people who have been started and then monitored for their response to initial statin treatment.
Amgen Ltd	Guideline	007	020	**Rec 1.6.14** Amgen supports the specification of clinical measurements at 3 months, and an annual medication review. These are important elements in ensuring appropriate treatment and escalation of therapies according to clinical need.	Thank you for your comment.
Amgen Ltd	Guideline	008	001	**IND2022-133**	Thank you for your comment. The target in this guideline is based on both clinical and cost

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				Within primary care the existing QoF (https://www.england.nhs.uk/wp-content/uploads/2023/03/PRN00289-quality-and-outcomes-framework-guidance-for-2023-24.pdf) indicator has established 1.8mmol/l as the target for LDL management, consistent with AAC (Accelerated Access Collaborative), JBS3 (Joint British Societies for the prevention of cardiovascular disease) and ESC (European Society of Cardiology) guidelines. Amgen does acknowledge the creation of a new indicator intended for introduction to QoF however the shift to 2.0mmol/l is likely to raise questions within primary care (non-specialist) practice around what the optimal level should be, and why discrepancies exist. Lipid management is an area that is perceived as complex in primary care. Much work has been done by the Accelerated Access Collaborative and AHSN network over recent years in simplifying and raising awareness of lipid management pathways, all based on a treatment target of 1.8mmol/l. Changing the incentivised measure for primary care to 2.0mmol/l is likely to lead to confusion as to the optimal level for LDL cholesterol. Furthermore, while it may be intended that QoF is updated with the new indicator, this will not take place until April 2024 at the earliest, meaning an overlap of three months during which QoF will still incentivise 1.8mmol/l against CG181's target of 2.0mmol/l.	effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The proposed indicator is based on NICE recommendations for a lipid target. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator.

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				Amgen recommends maintaining the NICE indicator at 1.8mmol/l to help ensure consistency of implementation of the guideline, as this will avoid any confusion within primary care as to optimal treatment. GPs and primary care clinicians who explore other guidance will encounter clinical evidence (AAC, JBS3, ESC) identifying 1.8mmol/l as the suggested treatment target for the secondary prevention cohort.	
Amgen Ltd	Guideline	General	General	Amgen welcomes the intention behind this guideline to improve the management of cholesterol in people at high risk of major cardiovascular events. The treatment and management of lipids is an area which is often perceived as complex and can result in variable implementation so the focus on improving consistency in practice is timely. Amgen supports the principle that clinicians are given freedom to make decisions about treatment in conjunction with patients, and to determine which treatment options may deliver the best clinical outcomes on an individual basis. We believe the guideline could go further in its ambition to treat people at high and very high-risk of major cardiovascular events, notably through lowering the target for treatment and encouraging a preference for LDL (low-density lipoprotein) testing to support evidence-based practice in optimising treatment.	Thank you for your comment. The target is based on clinical and cost effectiveness to ensure the optimal allocation of NHS resources. The recommendations do not preclude the use of clinical judgement to aim for a lower target on an individual patient basis (see recommendation 1.7.11).
Association for Clinical biochemistry and	Guideline	005	005	Section 1.6.1 • The increase in the standard CVD secondary prevention target LDL cholesterol from 1.8 to 2.0	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness, with data from clinical trials informing the economic modelling, to ensure the optimal allocation of

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laboratory medicine (ACB)				mmol/L, which seems to have been recommended primarily for cost reasons. • It is well established that "the lower the better" regarding LDL-C, in those with CVD. European targets (ESC/EAS) for secondary prevention are lower than our current LDL-C target, at 1.40 mmol/L. Increasing our current threshold feels like a step backwards in managing one of the major risk factors in this significant cause of morbidity/mortality. LDL-C targets have shown year-on-year reductions as evidence has grown. How can we justify this step backwards? • I feel this change in the secondary prevention target shows a lack of ambition and it will lead to less robust risk factor management in those with existing CVD, increasing the likelihood of recurrent events. In those with CVD and multiple risk factors e.g. diabetes or smoking, it is imperative LDL-C is reduced robustly, as entry via the endothelium to form plaque is easier and therefore a relaxed LDL-C target would adversely impact such patients. • The emphasis on using a non-HDL cholesterol target (of 2.6 mmol/L) rather than a LDL cholesterol target value, when the evidence base is primarily for LDL cholesterol and other NICE guidance (technology appraisals) for use of newer	resources for the NHS. The cost per QALY of a target of 1.8 (used in the QoF) compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review DA and the committee discussion of the evidence. Recommendation 1.7.11 recommends that Ezetimibe is considered to reduce CVD risk further, even if the target is achieved. The LDL target is emphasised because the evidence was more robust but a non-HDL target is also given.

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				agents (such as PCSK9 inhibitors) is based on the LDL cholesterol value.	
British and Irish Association of Stroke Physicians	Guideline	005	005	We strongly encourage NICE to consider revising the targets to non-HDL-C 2.5 and LDL-C 1.8 mmol/l. • The draft guidance is not consistent with the NICE-endorsed NHSE/ACC pathway. Doctors and policy makers have spent the last 3 years educating GPs and healthcare professionals on this pathway. • The draft guidance is not consistent with latest ESC/EAS guidelines and AHA/ACC guidelines which use LDL 0.8 and non-HDL-C 2.5/2.6 targets. • The draft guidance is not consistent with QOF of LDL-C 1.8 target • The draft guidance is not consistent with the 2023 National Stroke Guideline which uses LDL-C target of 1.8, based on the Treat Stroke to Target trial. • The draft guidance is not consistent with the AHSN lipid pathways for ACS and Stroke, also uses LDL-C of 1.8. • The draft guidance is not consistent with JBS3 which uses non-HDL-c 2.5 and LDL-C 1.8, soon to be JBS4. We feel the LDL target of 2.0 cannot be justified on the cost-effectiveness argument as the vast majority of people	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. Cost effectiveness has not been considered by other guidelines. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. Recommendation 1.7.11 recommends that ezetimibe can be considered to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is achieved.

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				will achieve LDL-C of 1.8 on cheap, safe, effective, generic drugs i.e. statins and ezetimibe.	
British and Irish Association of Stroke Physicians	Guideline	007	014	It is unclear why NICE has chosen a threshold for Inclisiran use of LDL-C 2.6 mmol/l when most people would achieve an LDL-C of 1.3 mmol/l.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. A lower target was not shown to be cost effective. For example, the cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. We have edited recommendation 1.7.11 to make it clear that Ezetimibe could be considered to reduce CVD risk further. This would depend on several factors and would be discussed as part of shared decision making with the person. The recommendation is aimed at people who have been started and then monitored for their response to initial statin treatment.
British and Irish Hypertension Society	Guideline	005	005	Section 1.6.1: The BIHS are concerned that NICE and QOF are recommending different non-HDL and LDL targets (NICE, non-HDL < 2.6 or LDL < 2.0 versus the latest QOF indicator CHOL002 non-HDL < 2.5 or LDL <	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was

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				1.8). This is likely to cause confusion and lead to implementation inertia in clinical practice.	considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator.
British Medical Association	Guideline	005	005 – 007	We would support this target as it is felt that it would be beneficial for GPs to have an absolute level	Thank you for your comment.
British Medical Association	Guideline	005	014	This needs to ensure that practices are not penalised in any associated targets for adopting patient choice in the prescribing of this	Thank you for your comment. The recommendations do not preclude patient choice being considered when deciding on a target for an individual.
British Medical Association	Guideline	006	027	Ezetimibe has not been routinely prescribed in General Practice. Adding this and Inclisiran would therefore represent a significant change in practice	Thank you for your comment. Increased uptake of statins, ezetimibe and other lipid-lowering treatments will result in higher medication and monitoring costs to the NHS. It will also contribute to increased workload burden in primary care GP practices and pharmacies and in laboratories processing monitoring tests. The committee agreed this increase is necessary for downstream improvements in population health and the extra cost of lipid-lowering treatment would be partly offset by savings due to a reduction in CVD events (including admissions for stroke or heart disease and cardiovascular procedures).

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British Medical Association	Guideline	007	002 – 003	This should be clearer that where this has been commissioned as this is a red listed drug in most areas and it's limiting in NICE guidance does not change that status.	Thank you for your comment. NICE recommendations do not refer to whether a drug is red listed but prescribing should be in accordance with NHS guidelines.
British Medical Association	Guideline	007	005	The circumstances of why and when Ezetimibe should be considered should be made clearer	Thank you for your comment. We have edited recommendation 1.7.11 to make it clear that ezetimibe could be considered to reduce CVD risk further. This would depend on several factors and would be discussed as part of shared decision making with the person.
British Medical Association	Guideline	007	009	Whilst some practices do already offer Ezetimibe for patients not tolerating a statin, it is not routinely offered by many practices, so this would represent a large amount of work in many areas	Thank you for your comment. Increased uptake ezetimibe will result in higher medication and monitoring costs to the NHS. It will also contribute to increased workload burden in primary care GP practices and pharmacies and in laboratories processing monitoring tests. The committee agreed this increase is necessary for downstream improvements in population health and the extra cost of lipid-lowering treatment would be partly offset by savings due to a reduction in CVD events (including admissions for stroke or heart disease and cardiovascular procedures).
British Medical Association	Guideline	008		IND2022-133 The primary concern with the proposed indicators is the availability of a commissioned service r specific funding for Inclisiran as this is a significant piece of work that would overshadow any incentives provided through QOF	Thank you for your comment. NICE have no role in QOF negotiations.

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British Medical Association	Guideline	014	022	This needs clarification of what 'not appropriate' should include, for example: declines further treatment, cannot tolerate treatment/max tolerated, or where no Inclisiran service exists.	Thank you for your comment. Personalised care adjustments could be used to exclude patients from indicator denominators dependent on individual circumstances. Examples of these are included in the indicator specification and have been amended following this consultation.
British Medical Association	Guideline	015	017	This cannot be done in the timeframes suggested as general practice will not be ready in less than 6 months to prescribe Inclisiran.	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned'.
British Medical Association	Guideline	016	002	1.6.14 With regards to measuring Trigliceride levels, it is only clear if this done when the patient is fasting and would be inaccurate otherwise. This therefore has significant resource implications for practices.	Thank you for your comment. Recommendation 1.11.1 has been edited and now recommends a full lipid profile which could be non-fasted or fasted.
CaReMe UK	Cost utility analysis	007	016	The pathway illustrated in figure 1 does not accurately reflect the lipid lowering pathways recommended by the Accelerated Access Pathways nor clinical practice. There is not a serial treatment escalation approach of statin therapy, followed by statin+ezetimibe, followed by injectable therapies. In practice, a clinical judgment is made after statin therapy based on LDL-cholesterol level achieved and the likely further reduction achievable with ezetimibe. In many cases, clinicians move from statin to statin+injectable therapy to meet existing lipid thresholds and to maximise LDL-cholesterol reduction. This is fully aligned to Accelerated Access collaborative and NICE TAs	Thank you for your comment. We have revised Figure 1 so that it more accurately reflects the national pathway. We acknowledge that not everyone above the target will be escalated to ezetimibe. We have maintained this in the model base case, as this was the most cost-effective pathway. However, we have added sensitivity analyses to the model, where alternative treatment pathways were followed. In two of these analyses, the optimal target remained the same. In a third, the optimal target was slightly higher. The committee decided to stick with the target of 2.0 mmol per litre for LDL cholesterol.

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					The recommendation to offer ezetimibe plus a statin has been removed to avoid any potential conflict with the relevant NICE technology appraisals and to make it clear that we are not recommending a treatment pathway. Recommendation 1.7.10 now recommends that additional lipid lowering treatments should be offered and refers to the TAs on these. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
CaReMe UK	Cost utility analysis	General	General	Because of the points raised in comment 4, the cost effectiveness analysis is flawed and the output cannot be considered reliable.	Thank you for your comment. We acknowledge that not everyone above the target will be escalated to ezetimibe. We have maintained this in the model base case, as this was the most cost-effective pathway. However, we have added sensitivity analyses to the model, where alternative treatment pathways were followed. In two of these analyses, the optimal target remained the same. In a third, the optimal target was slightly higher. The committee decided to stick with the target of 2.0 mmol per litre for LDL cholesterol. The committee decided to focus on recommending a target and do not recommend a treatment sequence for people above the target.
CaReMe UK	Guideline	005	005 – 007	We urge the committee to retain non-HDL-cholesterol and LDL-cholesterol numerical targets which are consistent with current international guidelines and or the recently	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of

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				adopted QOF indices. Effective lipid lowering in clinical practice is already jeopardised by the presence of the various targets and thresholds for treatment initiation which are discrepant across NICE Guidance, ESC and AHA guidance. Introducing new numerical targets based on cost-effectiveness modelling is likely to increase confusion and reduce attainment of lipid goals.	resources for the NHS. This guideline is the only one that has made a recommendation on the target for the secondary prevention of CVD. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator.
CaReMe UK	Guideline	005	005 – 007	We disagree with the decision to set the targets at non-HDL cholesterol levels of 2.6 mmol/litre or less, or where non-HDL is not recorded, LDL 6 cholesterol levels of 2.0 mmol/litre or less. We appreciate that these values were derived from health economic modelling, however we do not agree that values derived from modelling should take precedence over those used to define entry into large, properly conducted randomised clinical trial. We argue that thresholds for which there is clinical trial evidence of benefit should be employed – for example LDL-cholesterol 2.6mmol/L or greater for inclisiran, based on enrolment in ORION-11.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. The health economic model was informed by a network meta-analysis of the relevant clinical trials including ORION-11.

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CaReMe UK	Guideline	005	005 – 007	We welcome the decision to set numerical target values for lipid lowering therapy in secondary prevention rather than a percent reduction from baseline. This is much more 'user friendly' for the scenario in which HCPs practice, in which baseline lipid values are often unavailable.	Thank you for your comment.
Daiichi Sankyo UK Ltd	Economic model	General	General	**[This text was identified as confidential and has been removed].**	Thank you for your comment. 1. The estimate of 15% for statin intolerance is for a broader population. The committee concluded that people with CVD are more tolerant of statin side effects and that the estimate of 9.1% based on a recent systematic review is plausible. 2. We already acknowledge the lack of data on the cholesterol distribution as a limitation. 3. We now acknowledge that some people in the trials were on a low dose statin. 4.We have now subtracted the cost of ezetimibe, so that the model assumes use of the combined pill. 5. For CLEAR-Outcomes, we continue to use 20.3%, as this adjusted estimate was the primary trial outcome. We also note that CLEAR-Outcomes was in a CVD population; CLEAR-Tranquillity was not. However, we acknowledge that in CLEAR-Outcomes

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					few people had a background of ezetimibe, which is a limitation from the point of view of the model. Therefore, we have changed the effect size in the analysis to be 24.4%, which is the mid-point of both trial estimates. Data from other trials included in the NMA had also been subject to a similar adjustment according the trial protocols. This included ODYSSEY COMBO I and II, ODYSSEY KT, ODYSSEY LONG TERM, ODYSSEY DM insulin and dyslipidaemia and ODYSSEY EAST. 6. Thank you for alerting us to the 2015 CTTC paper. That analysis only included one additional trial, CORONA. That trial was in a heart failure, population. The committee specifically did not include heart failure patients in the model on the basis that they get less benefit from lipid lowering therapy. The committee therefore decided to continue to use the pooled effects from the 2010 paper in the economic model. We re-ran the sensitivity analysis with the revised price and effect size for BA. The cost-effective target has not changed.
Daiichi Sankyo UK Ltd	Evidence Review - D	055	032 - 040	It is acknowledged in this section by the committee that no review of the evidence from TA694 or CLEAR Outcomes has been undertaken as part of this guideline update. There are number of statements published in this section	Thank you for your comment. The committee reviewed the baseline characteristics of the included participants and noted that only 11.5% were receiving ezetimibe, which was thought to be suboptimal.

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				about the CLEAR Outcomes study which DSUK would like to provide feedback on. It is stated that there is a potential over-estimation of the effectiveness of bempedoic acid in the Cardiovascular Outcomes study. This is stated "*as a result of the control arm population not being on optimal lipid lowering therapy*". One of the inclusion criteria of CLEAR Outcomes was that patients had to have stable and optimised therapy.[1] The addition of other lipid lowering therapies (LLTs) during the Outcomes study in the placebo arm meant there was a reduced absolute LDL-C reduction between the control and study arms over time. The time-averaged LDL-C reduction (15.9%) vs placebo does correlate with the expected relative reduction in MACE as per CTTC. The MACE reduction potential of BA is therefore potentially under-estimated for this reason as 6 months reduction LDL-C (21.1%) was not maintained over the course of the study. In the study, the incidence of a primary end-point event was significantly lower with bempedoic acid than with placebo (819 patients [11.7%] vs. 927 [13.3%]; hazard ratio, 0.87; 95% confidence interval [CI], 0.79 to 0.96; P = 0.004), as were the incidences of a composite of death from cardiovascular causes, nonfatal stroke, or nonfatal	The estimate was taken from the CLEAR Outcomes trial because the population in that study most closely matched the population of interest in our analysis. Specifically, the majority had a previous CVD event (secondary prevention population), unlike the CLEAR Tranquillity study, in which only 26% had CVD. Additionally, TA694 only recommends bempedoic acid if statins are contraindicated or not tolerated, but 31% of participants in CLEAR Tranquillity were taking low dose stains (rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, pitavastatin 2 mg), whereas CLEAR Outcomes only permitted very low dose statins. As you say, the estimate used from CLEAR Outcomes is the 6 month time point adjusted for baseline LDL cholesterol or glycated haemoglobin levels with the use of a pattern-mixture model for missing data. This was the pre-specified primary LDL-C analysis in the trial protocol, and as such was considered the most appropriate value to use (in preference to the observed values which was listed as the secondary/supportive method of data handling for this outcome). Given the limitations of both trials, in the guideline's economic model we have now used an average effect size from CLEAR Outcomes and CLEAR Tranquillity.

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				myocardial infarction (575 [8.2%] vs. 663 [9.5%]; hazard ratio, 0.85; 95% CI, 0.76 to 0.96; P = 0.006); fatal or nonfatal myocardial infarction (261 [3.7%] vs. 334 [4.8%]; hazard ratio, 0.77; 95% CI, 0.66 to 0.91; P = 0.002); and coronary revascularization (435 [6.2%] vs. 529 [7.6%]; hazard ratio, 0.81; 95% CI, 0.72 to 0.92; P = 0.001).[2] BA had no significant effects on fatal or nonfatal stroke, death from cardiovascular causes, and death from any cause. The incidences of gout and cholelithiasis were higher with bempedoic acid than with placebo (3.1% vs. 2.1% and 2.2% vs. 1.2%, respectively), as were the incidences of small increases in serum creatinine, uric acid, and hepatic-enzyme levels. [2] Analysis published by the Cholesterol Treatment Trialists' Methodology showed that normalized Hazard Ratios for individual endpoints of major coronary events, non-fatal MI, revascularization, and stroke for BA vs placebo in CLEAR Outcomes were comparable to the risk ratios for those endpoints with statins in the CTT meta-analyses.[3] The time-averaged LDL-C reduction in the CLEAR Outcomes study correlates with the proportional reduction in MACE which is comparable with CTTC. It is also stated in this section that the "*mean age of the people in this trial was lower than those in who the drug would be offered in clinical practice, so the incidence of*	We have now clarified that the people who experience renal adverse events were withdrawn from BA before any serious complication had occurred. However, the committee still consider this an important caution. We have also clarified that the mean age of the population in the trial was 7 years younger than the CPRD population used to inform the guideline model.

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				adverse events may be higher, and a proportion are likely to be unable to tolerate bempedoic acid". The mean age of participations in CLEAR Outcomes was 65.5+/- 9 years (SD), which is consistent with mean ages for lipid lowering treatment.[1] This is evidenced in Ray et al (2021)'s observational EU-wide Da Vinci study, which explores treatment patterns across primary and secondary prevention, in which the mean age was 65 (12 SD; 63 primary prevention and 68 Secondary prevention).[3] Additionally, the mean participant age in the SANTORINI multi-national observational study for secondary prevention was 66.[4] On line 36, page 55, it is stated: *The committee also noted the high incidence of renal adverse events 37 in CLEAR Outcomes, but how to monitor for these is currently unclear.* The definition of renal impairment in the study included: eGFR <15 mL/min/1.73 m2 eGFR 15 to <30 mL/min/1.73 m2 Creatinine >1 mg/dL change from baseline Creatinine >0.5 mg/dL change from baseline Creatinine increase from baseline >30% within 4 weeks (30 days) after first dose of IMP BUN (blood urea nitrogen) doubled post baseline	

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				BUN/creatinine ratio or eGFR change >30% from baseline. The following is taken from the Section 4.8 of the bempedoic acid SPC for completeness:[6] Bempedoic acid has been shown to increase serum creatinine and BUN. In the pooled placebo-controlled trials, a mean increase of 0.05 mg/dL (4.4 micromole/L) in serum creatinine and a mean increase of 1.7 mg/dL (0.61 mmol/L) in BUN compared to baseline was observed with bempedoic acid at week 12. The elevations in serum creatinine and BUN usually occurred within the first 4 weeks of treatment, remained stable, and returned to baseline following discontinuation of treatment. The observed elevations in serum creatinine may be associated with bempedoic acid inhibition of OAT2-dependent renal tubular secretion of creatinine (see section 4.5), representing a drug-endogenous substrate interaction and does not appear to indicate worsening renal function. This effect should be considered when interpreting changes in estimated creatinine clearance in patients on Nilemdo therapy, particularly in patients with medical conditions or receiving medicinal products that require monitoring of estimated creatinine clearance.	

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				[1] Nicholls, Stephen J, et al, 2020. Rationale and design of the CLEAR-outcomes trial: Evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance. *American Heart Journal*. Volume 235. 104-112. [2] Nissen et al, 2023. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med 2023.* 388:1353-1364 [3] Lincoff et al. Comparison of the Cardiovascular Benefits of Bempedoic Acid with Statins—Analysis by the Cholesterol Treatment Trialists' Methodology. Available: https://www.newswise.com/pdf_docs/168625632780589_Lincoff%20Abstract.pdf (Accessed: October 2023) [4] Ray et al, 2021. EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. *European Journal of Preventive Cardiology* 28. 1279–1289. [5] LDL-C goal achievement and lipid-lowering therapy in patients by atherosclerotic cardiovascular disease subtype: the SANTORINI study. Preventive Cardiology – Risk Factors and Prevention, Lipids. ESC Congress 2022 – Barcelona, Spain, August 2022. [6] Nilemdo (Bempedoic acid) 180mg film-coated tablets. Available: https://www.medicines.org.uk/emc/product/11743/smpc#gref	

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Daiichi Sankyo UK Ltd	Evidence Review - D	055	015	Typo on line 15, where the correct coding for technology appraisal for bempedoic acid is TA694, not TA684.	Thank you for your comment. This has been corrected.
Daiichi Sankyo UK Ltd	Guideline	007	009	1.6.12 The approach to defining statin intolerance as a patient population which cannot tolerate statin of any intensity or dose is impractical, not consistent with NICE-accredited guidelines, and in the views of DSUK inconsistent with the recommendations of TA694. Elsewhere in the draft proposals it is acknowledged on page 11 (lines 19-22) that the "*committee did not review the evidence for the clinical effectiveness of lipid-lowering treatments in people who are statin intolerant or for whom statins are contraindicated, but based their recommendations on the NICE technology appraisals on inclisiran, bempedoic acid, evolocumab, and alirocumab."* As the recommendations at based on existing Technology Appraisals, DSUK requests consistency in wording when outlining recommendations for patients determined to be statin intolerant. "*Offer ezetimibe instead of a statin"* and *"it is recognised that the person cannot tolerate statins of any intensity or dose*", should be changed to one of the following possible alternatives:	Thank you for your comment. The evidence for bempedoic acid was not reviewed in this guideline update and the recommendations were based on the technical appraisal (TA694). This states that bempedoic acid is recommended only if statins are contraindicated or not tolerated [and] ezetimibe alone does not control low-density lipoprotein cholesterol well enough. This therefore does not include the option for the person to be on a low intensity statin.

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				"*Offer ezetimibe, either instead of, or in combination with, a low-dose statin/low-intensity statin as defined in the NICE-accredited AAC pathway*" OR; *Offer ezetimibe, if after documented discussion of the strategies outlined in recommendation 1.6.6, it is recognised that the person is statin intolerant (unable to tolerate more than low-intensity statin as defined in the AAC pathway)."* OR; *Offer ezetimibe, if after documented discussion of the strategies outlined in recommendation 1.6.6, it is recognised that the person is statin intolerant"* DSUK believes that the above considerations would deliver the objectives of ensuring cost-effective treatment escalation, whilst remaining consistent with the wording in TA694. NICE may wish to go a step further and add a list within the TA694 recommendation clarifying the study populations which were evaluated by NICE that included	

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				proportions which were receiving low-to-very-dose statins at baseline. [1] NHS England, 2022. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. Available: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-v6.pdf (Accessed: October 2023).	
Daiichi Sankyo UK Ltd	Guideline	007	014	1.6.13 The wording for line 1.16.13 outlines an equitable approach to treatment sequencing based on shared-decision making and consideration of the relevant individual NICE technology appraisals for later-lines of lipid lowering therapy. The justification given throughout the consultation document is that NICE has not undertaken a cost-effectiveness analysis comparing these technologies. Daiichi Sankyo UK would like to outline the practical case for why the recommendations in TA694 should be considered preferentially, ahead of the other technology appraisals, in the statin intolerant sub-population: • Bempedoic acid (BA) with ezetimibe within its full TA694 recommendation has no LDL-C threshold	Thank you for your comment. The committee did not review the evidence on statin intolerance and referred to the technology appraisals on the relevant treatment options. Bempedoic acid with ezetimibe, evolocumab (with other lipid lowering therapies) and inclisiran (with other lipid lowering therapies) are all treatment options if the target is not reached on ezetimibe alone. The TAs in recommendations 1.7.10 and 1.10.2 are now listed in alphabetical order.

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				restrictions, compared to inclisiran (2.6 LDL-C), and the PCSK9is alirocumab and evolucumab (3.5 LDL-C), respectively • DSUK would request that given the central focus of this guideline is on reaching a defined target LDL-C level, minimal LDL-C eligibility thresholds should be made clear to guidelines users when considering therapy escalation beyond statin and ezetimibe to reach these guideline-recommended targets • BA with ezetimibe is recommended across both primary and secondary prevention cohorts for patients which are statin intolerant. Itis available as a fixed-dose combination, alongside separate monotherapy treatment options. The former is increasingly prescribed across NHS practice.[1] The cost for the fixed-dose option (retail price: £55.44) is a lower acquisition cost than two separate monotherapy tablets (£57.30). This assists in reducing pill burden for the patient, a point raised by in this guideline on page 11; line 11 • BA's clinical appropriateness for statin intolerant patients is demonstrated through the CLEAR studies clinical trial programme [2],[3] which	

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				informed the recommendations in TA694, and is also supported more recently by the published CLEAR Outcomes study[4] which investigated the affect of bempedoic acid on cardiovascular outcomes in statin intolerant patients Whilst DSUK acknowledges that NICE has not undertaken an indirect treatment comparison comparing the cost-effectiveness of TA694, TA393, TA733, and TA394. However, we request that NICE considers the points above in its review of the final wording in this guideline update. DSUK would also point out the grammatical inconsistency in the sequencing of the Technology Appraisals listed above. These are listed first in alphabetical order on lines 15/16, and then listed in non-alphabetical order on lines 16/17. DSUK presumes the second sequencing is on order of recency of appraisal publication dates, however this is not fully explained. This risks confusion and could be perceived as a de facto recommendation on sequencing. [1] Daiichi Sankyo UK, 2023. Data on file. [2] Ballantyne et al., 2018. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. *Atherosclerosis*.277.195-203.	

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				[3] Laufs et al, 2019. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. *Journal of the American Heart Association*. 8(7); [4] Nissen, et al, 2023. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *New England Journal of Medicine*. 388:1353-1364 Banach M, Duell PB, Gotto AM Jr, et al. Association of bempedoic acid administration with atherogenic lipid levels in phase 3 randomized clinical trials of patients with hypercholesterolemia. *JAMA Cardiol.* Published online July 1, 2020. Doi:10.1001/jamacardio.2020.2314	
Daiichi Sankyo UK Ltd	Guideline	008	002	DSUK would recommend a definition of statin intolerance be added to the "terms used in this guideline" on page 8 (after "High-intensity statin"). For example, this could specify "after documented discussion of the strategies outlined in recommendation 1.6.6 and 1.6.7, the person cannot tolerate more than low-intensity statin. Low-intensity statins are defined in the NICE-accredited AAC pathway, published November 2022."[1] The importance of mirroring this AAC pathway is also highlighted in the Evidence Review D document, in which on line 11-12 (page 56) it is stated "the committee noted that there is guidance for people who are statin intolerant". In the accompanying statin intolerance pathway version of the AAC guideline, it is advised that *therapy with a lower*	Thank you for your comment. The recommendations refer to the technology appraisals on statin intolerance as the evidence was not reviewed by the committee. The criteria in whom to prescribe these treatments is contained within the technology appraisals. In 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024.

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				dose statin is preferred to no statin"[2]. This is a principle which should be aligned to the definitions outlined in CG181, rather than the absolutist version being proposed. If the definition of statin intolerance in the AAC pathway is insufficient in the context of this guideline, the guideline should state the basis for why statin intolerance means absolute statin intolerance, rather than partial.[3] [1] NHS England, 2022. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. Available: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-v6.pdf (Accessed: October 2023). [2] NHS England, 2022. Statin Intolerance Pathway. Available: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/statin-intolerance-pathway-v2.pdf (Accessed: October 2023) [3] NLA Scientific Statement on Statin Intolerance: A New Definition and Key Considerations for ASCVD Risk Reduction in the Statin Intolerant Patient. *J Clin Lipidol*. 2022; 9.	
Daiichi Sankyo UK Ltd	Guideline	011	028 - 030	The description of the economic model does not mention the inclusion of Bempedoic acid (BA) in the pathway. This is despite the fact that it was explored in a scenario analysis.	Thank you for your comment. The rationale has been revised and much of the detail about the health economic modelling has been removed for conciseness. The recommendations have been

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				The wording should recognise that a scenario analysis was performed in which statin intolerant patients received first ezetimibe and then ezetimibe plus BA, and then ezetimibe plus BA plus inclisiran. This could include text revisions on Page 11 as follows: *"The economic modelling included a scenario where bempedoic acid was added after ezetimibe and before inclisiran for people who are intolerant to statins or for whom statins were contraindicated and people were treated to the same lipid target as those on statins."*	revised so that treatment sequences are no longer mentioned, therefore, it is not necessary to justify any specific treatment sequences in the rationale. The revised rationale does not refer to the position of BA in the pathway in the economic analysis but nor does it refer specifically to the position of other medicines in any of the pathways that were modelled. Description of the pathways remains in the committee discussion of the evidence section of Evidence Review E and in the economic analysis report.
Daiichi Sankyo UK Ltd	Guideline	012	005 - 006	DSUK questions the assumptions within the assumed statin intolerant population, which is quoted at 9.1%. A 2019 Delphi Panel, a widely accepted method for achieving convergence of opinion concerning real-world knowledge solicited from experts, found that statin intolerance was considered to be at 15% across the UK, with 35 per cent of those receiving ezetimibe and 64% not considered at goal.[1] These eligible patient estimates (85,949) were accepted by NICE as part of the appraisal for bempedoic acid and similar numbers were quoted by NICE in their press release at point of Final Appraisal Determination (FAD) publication. The number could be even higher as the rate-	Thank you for your comment. We understand that the estimate of 15% for statin intolerance is for a broader population. The committee concluded that people with CVD are more tolerant of statin side effects and that the estimate of 9.1% based on a recent systematic review is plausible. Note that the figure of 9.1% has been removed from the rationale, as it is not considered critical in justifying the target. However, the rationale for using this figure remains in the model report.

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				limiting step is the number treated with ezetimibe monotherapy, which is recognised in the guideline as an underutilised treatment strategy. Bilitou et al (2019) also reported in a CPRD dataset analysis that "More than half of patients (52.7%, n=147,201) in the overall cohort had a code for statin intolerance, history of a code for conditions where statins would be contraindicated, or a code for adverse events related to statin intake after statin prescription"[2] DSUK would request that any statement concerning the percentage of statin intolerance across the statin-initiated population is reviewed. [1] Llewellyn, et al. Treatment patterns and healthcare resource use in primary hypercholesterolaemia and mixed dyslipidaemia: results of a UK Delphi panel. *Poster presentation at 88th EAS Congress, 2020.* (Accessed: October 2023) [2] Bilitou et al, 2019. Prevalence and Patient Outcomes of Adult Primary Hypercholesterolemia and Dyslipidemia in the UK: Longitudinal Retrospective Study Using a Primary Care Dataset from 2009 to 2019. *ClinicoEconomics and Outcomes Research*.14 189–203. (Accessed: October 2023)	

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Daiichi Sankyo UK Ltd	Guideline	012	006 - 007	*"Therefore, the committee agreed that the target for people who cannot take statins should be the same as for those who can take statins."* This wording should be amended to recognise that patients defined as statin intolerant may receive also receive a low-intensity statin, consistent with TA694 and/or the AAC pathway definitions. The following change to the wording is proposed: *"Therefore, the committee agreed that the target for people who <u>are statin intolerant</u> should be the same as for those who <u>are not statin intolerant</u>."*	Thank you for your comment. This phrasing is consistent with NICE TA694 on bempedoic acid.
Daiichi Sankyo UK Ltd	Guideline	General	General	It is positive that following feedback pre-consultation during the summer of 2023, the guideline committee has now integrated the use of Bempedoic acid (BA) as outlined in Technology Appraisal (TA694). Whilst we welcome the addition of BA to this section of the guideline, DSUK does wish to include further comments to inform the consultation process and the committee's decision-making. The current wording in this guideline suggests in several places that BA may only be used in patients receiving no statin of any intensity or dose. We believe that this is	Thank you for your comment. The evidence for bempedoic acid was not reviewed in this guideline update and the recommendations were based on the technical appraisal (TA694). This states that "bempedoic acid is recommended only if statins are contraindicated or not tolerated [and] ezetimibe alone does not control low-density lipoprotein cholesterol well enough". This therefore does not include the option for the person to be on a low intensity statin. In addition, TA694 states that: "During the appraisal, the company decided that it was no longer seeking a recommendation in the maximally tolerated statin

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				inconsistent with the recommendations outlined in TA694. All submitted comments in this form from DSUK will seek to explain the evidence base for this position. In summary, DSUK requests that sections of the wording in the CG181 *escalation of therapy* guideline should be revised to recognise that BA may be used in defined statin intolerant patients that are either receiving no or low dose statin, in line with the evidence underpinning the NICE recommendation in TA694, specifically CLEAR Tranquility[1] and CLEAR Serenity[2], as well as the recently published CLEAR Outcomes study.[3] In the first two reference studies, patients could only be enrolled if they were treated with a maximally tolerated dose of no more than low-dose statin or very-low-dose statin. In CLEAR Tranquility, all patients were also on background ezetimibe of 10 mg once daily, consistent with the recommendations in TA694.[1] A summary of the permitted qualifying doses of statin (daily dosing) across these 24-week CLEAR Serenity and 12-week CLEAR Tranquility studies is presented in the Banach pooled analysis (2020) referenced below.[3] Furthermore, as recognised in Table 19 of the Economic Report for the guideline, 22.7% of patients in the CLEAR Outcomes trial were receiving a very-low dose statin at baseline (an average daily dose of rosuvastatin <5 mg,	population (populations 4a and 4b), because the incremental cost-effectiveness ratio (ICER) estimates were too high to be recommended for routine use in the NHS." The clinical and patient experts agreed with the position of bempedoic acid proposed by the company Whilst the committee understand the reality of some patients not being eligible for injectables or bempedoic acid, the actual decision about prescribing will be individualised. However, NICE needs to be consistent and the guideline therefore cannot contradict recommendations from any of the existing TAs. In 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator

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				atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg). As reported in the DSUK original NICE submission in 2019 (Table 13), 32.6% of patients in CLEAR Tranquility and 7.7% in CLEAR Serenity received statin therapy at baseline. The cost-effectiveness of bempedoic acid assessed in TA694 was based on efficacy observed in CLEAR Tranquility and CLEAR Serenity and reflects this use of low- or very-low dose statin in a proportion of patients. DSUK believes that the wording of the guidance in TA694 does not specify that statin therapy should be discontinued or that patients must not receive statin therapy or any intensity or dose. The existing proposed wording in the CG181 guideline update for escalation of therapy of statin intolerant patients suggests the opposite. Whilst the use of such low-dose statins in clinical practice varies extensively, clinical evidence exists to show that such doses are preferable to no statin treatment in all circumstances.[4] This is confirmed by the amended statement in the CG181 update in line 21 on page 6, which states physicians should "Advise the person that any statin at any dose reduces CVD risk". The definitions of low-intensity/low-dose statin in the NICE-accredited Accelerated Access Collaborative (AAC)	specification will be shared with NHS England to consider alteration to the existing QOF indicator

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				lipid management pathway[4], do not align precisely align with the permitted doses in the relevant CLEAR studies. However, differences between the AAC pathway and the trials underpinning the recommendation in TA694 are small. Rosuvastatin 5mg and atorvastatin 10mg were permitted in CLEAR Tranquility and CLEAR Serenity but are classified as medium intensity in the AAC pathway. Otherwise, the definition of low intensity statin in the AAC pathway is consistent with the statins received in CLEAR Tranquility and CLEAR Serenity. DSUK request that efforts should be made to ensure that the population for whom bempedoic acid is recommended in TA694, which DSUK believes includes a broader eligible population than patients not receiving low-dose statin at baseline, is reflected in the proposed treatment sequencing recommendations in this guideline. As a practical, conservative, and consistent approach, DSUK would propose that NICE recognises that patients receiving no or low-intensity statin (as defined in the NICE-accredited AAC pathway) may be escalated to bempedoic acid therapy with ezetimibe, if clinically appropriate. This would be consistent with the trials underpinning the TA694 guidance, except that patients receiving rosuvastatin 5mg or atorvastatin 10mg would not be included in the guideline while they were included in the trials. It would also ensure that patients which are	

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				defined as statin intolerant have an opportunity to escalate on therapy should their non-HDL-C and/or LDL-C levels remain above the proposed target. There is a risk that the existing proposed wording, which suggests an absolutist interpretation of statin intolerance, leaves patients unable to reach guideline recommended targets. These patients may be ineligible to access later-line injectable therapies due to NICE criteria and local commissioning policies. Whilst small in the context of the overall guideline consultation, for this group of statin intolerant patients who are not at target after initiated and managed with ezetimibe, and do not qualify for an injectable therapy based upon NICE's own eligibility criteria, there are very few alternatives available to support them. The proposed target LDL-C level proposed in page 5 (line 4), whilst inconsistent with recommendations in EAS/ESC 2019 guidelines around best practice lipid management, is a step in the correct direction to ensure all patients with elevate CV risk in secondary prevention can achieve lower consistent guideline-recommended goals. The committee should consider however the risk of confusion and inconsistent with 2019 EAS/ESC guidelines which recommends 1.8 for high CV risk and 1.4 for very high CV risk patients.[6] The target is also non-aligned with existing targets in the GP contract, and the targets suggested via	

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				the NICE-accredited AAC pathway.[4] Given the more frequent reporting of non-HDL-C levels in NHS clinical practice, and the current recommended target levels in QOF at 2.5 mmol/L non-HDL-C, DSUK would propose a pragmatic approach where the proposed target is reduced from 2.6 to 2.5. This would ensure consistency with current targets and should negligibly affect commissioning budgets and NHS resources. Finally, NHS England has outlined ambitions in various policy documentation to improve cardiovascular disease risk prevention management, with the headline national objective of 150,000 CV events being prevented by 2028 (publication: 2019).[7] This guideline will be an important lever towards supporting those objectives, subject to the feedback being included in the final version. [1] Ballantyne et al., 2018. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. *Atherosclerosis*.277.195-203. (Accessed: October 2023) [2] Laufs et al, 2019. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. *Journal of the American Heart Association*. 8(7); (Accessed: October 2023) [3] Banach, 2020. Pooled Analysis. Bempedoic acid safety analysis: Pooled data from four phase 3 clinical	

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				trials. *Journal of Clinical Lipidology*.14, 649-659. (Accessed: October 2023). (Accessed: October 2023) [4] NHS England, 2022. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. Available: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-v6.pdf (Accessed: October 2023). [5] Nissen, et al, 2023. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *New England Journal of Medicine*. 388:1353-1364 Banach M, Duell PB, Gotto AM Jr, et al. Association of bempedoic acid administration with atherogenic lipid levels in phase 3 randomized clinical trials of patients with hypercholesterolemia. *JAMA Cardiol.* Published online July 1, 2020. Doi:10.1001/jamacardio.2020.2314 (Accessed: October 2023) [6] Mach et al, 2019. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal. Available: https://academic.oup.com/eurheartj/article/41/1/111/5556353 (Accessed: October 2023) [7] NHS England. Long Term Plan. Available: https://www.longtermplan.nhs.uk/ (Accessed: October 2023)	

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Diabetes UK	Guideline	005	005	We are concerned that the use of a new lipid target is higher than existing European Society of Cardiology and ADA guidelines as well as NHS England on Lipid Management Pathway The evidence is overwhelming that a reduction in LDL to a level lower than proposed in this draft guideline reduces risk of future cardiovascular events and remains safe. We know from our insight work that the impact of cardiovascular disease on people living with diabetes is far reaching and significantly impacts on people's quality of life and their ability to work Reference lipid-management-pathway-v6.pdf (england.nhs.uk) Reference https://diabetesjournals.org/care/article/46/Supplement_1/S158/148038/10-Cardiovascular-Disease-and-Risk-Management Reference https://academic.oup.com/eurheartj/article/41/1/111/5556353 Reference https://academic.oup.com/eurheartj/article-abstract/41/1/111/5556353	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 (used in the QoF) compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. Recommendation 1.7.11 recommends that Ezetimibe is considered to reduce CVD risk further, even if the target is achieved.
Diabetes UK	Guideline	006	007	The language used in this recommendation could suggest that patients are at fault for not taking their medication.	Thank you for your comment. Recommendation 1.9.1 has been edited to make it more patient-centred. This

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				We know there are multiple factors that contribute to patient adherence and believe person centred language should be used to support patients to overcome barriers that are preventing them from achieving their lipid target.	guideline also cross-refers to the NICE guideline on patient experience (CG138) which makes recommendations on tailoring healthcare services for each patient and enabling patients to actively participate in their care and the NICE guideline on medicines adherence (CG76). Both these guidelines make recommendations on communicating with the person about issues such as adherence.
Diabetes UK	Guideline	007	020	We would suggest that the word within replace the word about within this recommendation i.e. '… LDL cholesterol within 3 months. Using the phrase 'about 3 months' can be very open to interpretation, meaning measurements may take place significantly after 3 months and risk patient safety and prevent patients being prescribed the most appropriate treatment for them. We would also recommend the level should be monitored annually thereafter as it will help monitor the patient's response to treatment and annually thereafter as it may help to monitor the response to therapy and inform treatment decisions.	Thank you for your comment. Recommendation 1.11.1 has been edit and now recommends at 2 to 3 months. Recommendation 1.11.9 now recommends that an annual full lipid profile should be offered.
Diabetes UK	Guideline	015	017	We wish to comment that the guidance recommendation 1.4.48 re cardiovascular care of people with type 1 diabetes, could be open to misinterpretation and it needs to be explicitly stated you are referring to cardiovascular care. We also believe young people with type 2 diabetes should be seen by specialist clinics and so not managed by primary care.	Thank you for your comment. This recommendation has not been updated as part of this update of the guideline.

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Diabetes UK	Guideline	General	General	We welcome guidance that seeks to improve uptake of lipid treatment to reduce cardiovascular disease risk in people living with diabetes. Every week diabetes leads to more than 770 strokes, 590 heart attacks and 2,300 cases of heart failure. Reference: NHS Digital (2019), National Diabetes Audit 2017–18 Report 2A: Complications and Mortality	Thank you for your comment.
Greater Manchester Integrated Care System - Manchester MOT	Guideline	007	020	Sec 1.6.14 Specify that a non-fasting sample is recommended for measurement	Thank you for your comment. Recommendation 1.11.1 has been edited and now recommends a full lipid profile which could be non-fasted or fasted.
Greater Manchester Integrated Care System - Manchester MOT	Guideline	007	021	Sec 1.6.14 Although appreciate that calculated LDL would be more routine practice, it may be appropriate to mention that a direct LDL-C may be available in some services	Thank you for your comment. Recommendation 1.11.1 now refers to a full lipid profile which can be non-fasted or fasted, and in the case of the latter direct LDL would be available.
Greater Manchester Integrated Care System – Manchester MOT	Guideline	005	005 – 007	Sec 1.6.1 – risk of confusion and inconsistencies due to the target levels for non-HDL and LDL cholesterol levels are not aligned to national guidelines and indicators: • The Joint British Societies (JSB3) Established CVD Recommendations JBS3 Risk Calculator states 'Statins should be prescribed with a 'lower is better' approach to achieve levels of at least <2.5 mmol/L for	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. Cost effectiveness has not been considered in other guidelines. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per

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				non-HDL-C (equivalent to <1.8 mmol/L for LDL-cholesterol).' • 2019 EAS/ESC guidelines for the management of dyslipidaemias ESC Guidelines on Dyslipidaemias (Management of) (escardio.org) defines LDL-C and non-HDL-C targets based on CV risk with the proposed NICE targets for LDL-C (≤2.0 mmol/L) and non-HDL-C (≤2.6 mmol/L) corresponding to moderate risk (i.e. LDL-C <2.6 mmol/L) to high risk (i.e. non-HDL-C <2.6 mmol/L) according to ESC guidelines • NHS England » Quality and Outcomes Framework guidance for 2023/24 Cholesterol Control and Lipid Management CHOL002. Percentage of patients on the QOF Coronary Heart Disease, Peripheral Arterial Disease, or Stroke/TIA Register, who have a recording of non-HDL cholesterol in the preceding 12 months that is lower than 2.5 mmol/L, or where non-HDL cholesterol is not recorded a recording of LDL cholesterol in the preceding 12 months that is lower than 1.8 mmol/L with rationale to ensure that all patients with established cardiovascular disease, are considered for intensification of therapy where there is an insufficient reduction in cholesterol with first line therapy, usually a statin. • NHS Accelerated Access Collaborative » Summary of national guidance for lipid management (england.nhs.uk) recommends 'If non-HDL-C baseline value is not available*, consider target non-HDL-C <	QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024.

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				2.5mmol/L (approximately equivalent to LDL-C < 1.8mmol/L) as recommended by Joint British Societies (JBS3)'	
Greater Manchester Integrated Care System – Manchester MOT	Guideline	005	018	Sec 1.6.3: Re-phrase 'Offer lifestyle advice and advise on appropriate lifestyle changes at the same time' rather than 'consider lifestyle changes at the same time if appropriate' as lifestyle modifications play a pivotal role in improving the lipid profile.	Thank you for your comment. Recommendation 1.7.4 has been edited to make clear that lifestyle changes should be discussed at the same.
HEART UK – The Cholesterol Charity	Guideline	005	004 – 007	Whilst we welcome the recommendation to have a numerical target for lipid levels as opposed to a percentage reduction, we are extremely concerned that the proposals in these draft guidance are for higher levels of LDL/non-HDL than the current targets approved by NICE through the AAC guidance and adopted into clinical practice through the Quality and Outcome Framework. NICE TAs are all based on LDL-C rather than non-HDL-C. NICE CG181 should follow the same. Almost all clinical trials recruited patients based on their LDL-C and CTT meta-analyses showed benefit related to absolute LDL-C reduction rather than percentage reduction (nor non-HDL-C),	The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The target is population based and the committee acknowledge that at the level of the individual it may need to be modified for example based on the individual's risk. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The new recommendations will be shared with NHS England to

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				We know from our helpline that patients want a clear target that is an absolute number rather than a percentage to understand the benefits to themselves as an individual. So, whilst patients certainly like the absolute numbers that NICE currently state, there will be complete confusion why NICE have changed their minds on the 1.8 mmol/L up to 2.0. We anticipate a lot of people contacting the HEART UK helpline as they will be rather concerned and even scared about their CVD risk being increased, particularly if they are at 1.4 mmol/L, which is the very high risk target in the EAC/EAS guidelines. Some patients may also decide to come off treatment as NICE have stated it's acceptable to have higher levels. This change we consider could have a huge backward step from a patient perspective and increase access to our helpline. Our Helpline team will find this change extremely difficult to explain, clarify and justify to the patients. From a patient perspective it is about their CVD health and not cost effectiveness for the system. Raising the thresholds would almost certainly revive unfounded concerns that lowering LDL-C too much, to values below 2.0, could in some way be hazardous. This would indeed be counter productive. The shortcomings of the Friedewald equation for calculation of LDL-C are well recognised, in particular it has never been validated in statin treated patients and it	consider update of the QOF. In 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. Recommendation 1.7.11 recommends that ezetimibe can be considered to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is achieved. The committee agreed that LD was the most robust measure in the economic model (see the committee's discussion of the evidence in evidence review D) but non-HDL is also given where a fasting blood test was not performed.

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				consistently underestimates LDL-C as measured by the beta quant reference procedure, even under strictly observed 10-14 hour fasting conditions applied in clinical trials. This underestimate is dependent on triglyceride concentrations and is exacerbated when blood is collected from patients who are improperly fasted or non fasting as is usual in routine clinical practice. The Sampson equation, developed by NIH from a large number of samples measured by betaquant, is much less prone to this underestimate and it has been validated in statin treated patients and for use in non-fasting samples, and should therefore be recommended for use if possible – many UK labs are now offering this. However, neither equation provides a more robust estimate of residual risk than non-fasting non-HDL-C which should remain the primary treatment target. It is unfortunate that the large CTT database, which contains individual TC, HDL-C and TG data as required to calculate LDL-C could not have been asked to provide the non-HDL-C data to more accurately model the risk reduction per mmol/L of non-HDL-C on statin treatment. Note that with an assumed low/normal TG of 1.7 Friedewald equation calculated VLDL-C (ie non-HDL-C – LDL-C difference) is 0.8 whereas with Sampson equation this is 0.6. However to change from 1.8/2.5 to 2.0/2.6, although trivial, comes across as de-escalation of treatment; instead the evidence reviewed by NICE should be taken as an endorsement of the existing thresholds we	

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				have incorporated into the existing, NICE endorsed AAC national pathway, but with greater emphasis on non-HDL-C unless diagnosing FH or assessing eligibility for TA therapies. Given that LDL-C in clinical practice is an underestimate, it would be appropriate to take account of this by keeping with the less than 1.8 mmol/L target while emphasising that this equates to less than 2.5 mmol/L non-HDL-C. To shift this threshold to equal or less than 2.6 mmol/L, an upward shift of 0.2 mmol/L simply to mirror the LDL-C threshold, seems rather perverse and likely to confuse those who have just recently become accustomed to NICE endorsed thresholds of 1.8/2.5. At the very least the modelling should be re-run to compare the effects existing thresholds with those proposed before pressing ahead with what seems like a rigid adherence to the outcome of an imperfect data analysis at the expense of clinical common sense The LDL-C target of 2.0 is out of line, and is moving further away from, all current NICE approved guidance, 2023 National Stroke guideline, international (EAS/ESC, AHA/ACC and others) guidance and national and international lipid pathways. The 2.0 mmol/L cannot be justified on the cost-effectiveness argument as the vast majority of people will	

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				achieve LDL-C of 1.8 on cheap, safe, effective, generic drugs ie. Statin and ezetimibe. Also, this could be seen as not the best use of taxpayers money having spent the last 3 years educating GPs and other healthcare professionals across England on this national lipid management pathway ESC/EAS and other international guidelines have a target for LDL-C for very high-risk patients (<1.4 mmol/L) and we would suggest this guideline should include this.	
HEART UK – The Cholesterol Charity	Guideline	005	010 – 014	Ezetimibe and/or Bempedoic Acid should be offered in addition to Atorvastatin, especially in patients who are unable to take Atorvastatin 80mg. You recommend this later in the draft guideline in section 1.6.11 on page 7.	Thank you for comment. The evidence for this recommendation was not reviewed as part of this update and the committee were therefore unable to make recommendations on initial therapy only when to escalate therapy.
HEART UK – The Cholesterol Charity	Guideline	006	004 – 025	Link this to the NICE Approved AAC guidance on statin intolerance and lipid management	Thank you for your comment. NICE guidelines are only able to cross-refer to other guidance produced by NICE.
HEART UK – The Cholesterol Charity	Guideline	006	007 – 012	Ezetimibe and/or Bempedoic Acid should be offered in addition to Atorvastatin, especially in patients who are unable to take Atorvastatin 80mg.	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid modification therapy. The committee were therefore unable to make recommendations on initial statin therapy.

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HEART UK – The Cholesterol Charity	Guideline	006 007	026 – 029 001 – 004	Points 1.6.9. and 1.6.10. Use of Ezetimibe a standard second line therapy could lead to more patients "in limbo" ie LDL-C levels of 2.2 – 2.6 mmol/L – not to target but not eligible for further therapy. Clinicians should be able to decide how best to treat the individual patient in front them, as published in the lipid management pathway. For example, for those at high risk there is an option to include a PSCK9i after maximally tolerated statin which aims to give >50% reduction in LDL-C vs. the 20% reduction with Ezetimibe. We strongly recommend this choice in the pathway is reflected in the guideline. 1.6.15 states a non-HDL test – to align with other documents this should be a full profile (fasted or unfasted per AAC and EAS statement mentioned above)	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to avoid any potential conflict with the relevant NICE technology appraisals and to make it clearer that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs. Recommendation 1.11.1 now refers to a full lipid profile which can be fasted or non-fasted.
HEART UK – The Cholesterol Charity	Guideline	007	001 – 004	It is very confusing to have different eligibility thresholds for different medications when the prime objective is to lower the cholesterol risk to the patients. One patient told us on the HEART UK Helpline 'I was told I have to have a heart attack before I can get access to a particular drug, this worries me as I am trying to manage this situation to reduce my CVD risk'. We also heard a patient telling us 'I was told to stop my medication to increase my cholesterol numbers so I could get access to	Thank you for your comment. The committee recognised that there are different LDL treatment thresholds in the TAs based on clinical and cost effectiveness. Recommendation 1.7.10 now recommends that additional lipid lowering treatments should be offered, and refers to the TAs on these, without implying a treatment pathway. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the technology appraisals.

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				a particular treatment'. Clearly this is totally unacceptable from HEART UK and a patient perspective.	
HEART UK – The Cholesterol Charity	Guideline	007	009	Add in 'or ezetimibe and Bembedoic acid'.	Thank you for your comment. Recommendation 1.10.2 now refers only to the technology appraisals including TA694 on bempedoic acid. This states that bempedoic acid should be given with ezetimibe.
HEART UK – The Cholesterol Charity	Guideline	007	020	Include non-fasting blood test.	Thank you for your comment. Recommendation 1.11.1 has been edited and now recommends a full lipid profile which could be non-fasted or fasted.
HEART UK – The Cholesterol Charity	Guideline	007	021	The word calculate should be changed to calculated. The result of the calculation should be provided back to primary care from the lab – Primary Care do not have time to do any calculation so this kind.	Thank you for your comment. Recommendation 1.11.1 now refers to a full lipid profile. This is defined in the 'terms used' section and the word calculate has been removed but it is expected that this calculation will be performed by the laboratory.
HEART UK – The Cholesterol Charity	Guideline	007	028	Rather than 'consider' this should recommend a blood test. A review without knowing patients lipid levels is of limited value.	Thank you for your comment. Recommendation 1.11.9 now recommends a full lipid profile should be offered.
HEART UK – The Cholesterol Charity	Guideline	General		The ambition of the NHS Long Term Plan is to prevent up to 150,000 heart attacks, strokes and dementia cases in the next 10 years, by 2029. We are 6 years away from this and there a lot still to do to reach this target and ultimately save the funds for the NHS. Also, to keep more families together.	Thank you for your comment. The aim of this guideline is to provide recommendations based on clinical and cost effectiveness for health professionals, patient and carers on escalating lipid lowering therapies for the secondary prevention of CVD in NHS settings. The scope of this update to the guidance was to determine thresholds for secondary prevention. While triglycerides and triglyceride-rich lipoproteins are

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				Discussions with healthcare professionals are clearly demonstrating that healthcare in England is largely looking to international guidelines because they are aimed at what is best for patients. Triglyceride is a cardiovascular risk factor and a marker of residual risk in statin treated patients. Triglycerides are not mentioned sufficiently enough in the document and should be mentioned from the start as they should be measured at the same time as the cholesterol levels. The measurements must include Triglycerides to properly understand the CVD risk. e. The cholesterol contained in the triglyceride rich lipoproteins will influence the overall non-HDL cholesterol if triglycerides are raised. A full lipid profile should be measured including triglyceride and LDL-cholesterol (calculated). It is not necessary to fast patients. The difference in fasting and no-fasting results is negligible in vast majority of patients. European Atherosclerosis Society recommends fasting is not routinely required for determination of a lipid profile (https://pubmed.ncbi.nlm.nih.gov/27122601/). Further, 1) there are alternative formula (other than Friedewald) to use like Martin and Sampson suitable for patients with high triglyceride levels and non-fasting samples. Laboratories should be encouraged to measure full lipid profile and consider alternatives to Friedwald formula to calculate LDL-C. It is very important to include LDL-C in	increasingly considered as potentially important in CVD risk, their evidence base is not as well established as for LDL-C. We do not have robust data showing that lowering of TGs improves CVD outcomes and therefore there is no data to make a threshold decision. The REDUCE IT trial improved outcomes in people with HTG, but the benefit was irrespective of starting TG or achieved TG levels. Nonetheless. we do emphasise measuring a full lipid profile and TG level - compared to prior guidance - to allow clinicians to monitor TGs. The recommendations consulted on form part of the guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification. Recommendations 1.12.5 - 1.12.7 (on omega 3 fatty acid compounds, and on combination therapy) in that guideline include reference to icosapent ethyl in line with TA805. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid modification therapy. The committee were therefore unable to make recommendation on LPa. As noted in our manual: https://www.nice.org.uk/process/pmg20/chapter/introduction the duration of the consultation depends on the size of the guideline work to be reviewed. Whilst

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				the lipid profile result 2) the wording from the AAC where they use both fasted and unfasted values Icosapent ethyl in line with TA805 is not currently considered. NICE CG181 should include Icosapent ethyl as a treatment option in statin-patients with high triglyceride in line with nice TA805. In fact, all lipid lowering medications with NICE TAs should be mentioned and included in CG181. LP(a) should be included, whilst there is no direct treatment other than Apheresis. It is an independent risk factor for CVD. It is empirical to manage the patient's CVD risk by managing the cholesterol. The NICE accredited 2023 National Stroke guideline includes the importance of measuring LP(a) and the LP(a) Taskforce LP(a) Call to Action sets out the reasoning for NICE to include measuring and managing LP(a) as well as all the other CVD modifiable risk factors as step towards reducing CVD rates. We believe that principle 3 Section 12 of NICE' Principles have not been followed. This consultation period has not been lengthy enough to truly understand the documentation and thinking behind the draft guideline. This was also not transparent, some info is only available on a confidential basis, and is incredibly confusing for	consultation on a new guideline or full update, consisting of 15 to 20 review questions, would usually last for 6 weeks, an update with only 1 or 2 review questions will normally have a 2-week consultation. We appreciate, and value, the commitment of stakeholder organisations in participating in the consultation process. Stakeholders are advised in advance of the expected consultation dates to enable them to prepare. To support preparation for this consultation the outline Economic plan and Review protocol were published in February, and information event, to which all stakeholders were invited, was held in April.

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				patients with very technical and large documents to read through.	
Hyperparathyroid UK Action4Change	Guideline	002		Paragraph 3 In agreement with the statement in paragraph three, 'Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.' We feel an amendment should be added to alert providers of healthcare to the cardiovascular risks of hyperparathyroidism, hypercalcemia and parathyroid hormone in the upper normal range.	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid modification therapy. The guideline committee was therefore unable to make recommendations on the assessment and monitoring of conditions associated with secondary cardiovascular disease.
Hyperparathyroid UK Action4Change	Guideline	004		1.1.2 'Prioritise people based on an estimate of their CVD risk before doing a full formal risk assessment. Estimate their CVD risk using CVD risk factors already recorded in primary care electronic medical records. [2008].' We strongly advise an addition to this recommendation to	Thank you for your comment. This recommendation was not identified as needing updating at the time of scoping. We will pass your comment to the NICE surveillance team which monitor key events relevant to the guideline.

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				check calcium and parathyroid hormone levels if not already recorded in primary care electronic medical records. Based on your recommendation in NG132, not to routinely test parathyroid hormone unless calcium exceeds 2.60mmol/L, and also extensive collective experiences of soft tissue calcifications from our members (approaching 4000), that there are many missed opportunities to prevent cardiovascular disease, which we believe is a priority of a guideline to assess risk. 'The Parathyroid Gland and Heart Disease' is the title of an extensive paper published in Apr-June 2017. Not a UK study, but in the absence of UK studies, how can its contents be ignored? i.e.: 'Recent clinical and molecular research has shown that direct and indirect actions of PTH also affect the heart and vasculature through downstream actions of G protein-coupled receptors in the myocardium and endothelial cells. Patients with disorders of the parathyroid gland have higher incidences of hypertension, arrhythmias, left ventricular hypertrophy, heart failure, and calcific disease which translate into increased cardiac morbidity and mortality. Importantly, clinical research also suggests that **early treatment of parathyroid disorders through medical or surgical management may reverse cardiovascular remodelling and mitigate cardiac risk factors**.'	

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Hyperparathyroid UK Action4Change	Guideline	004		1.6 'Identifying and assessing cardiovascular disease risk for people without established cardiovascular disease' We are very concerned about failure to include any mention of **hypercalcemia**, **hyperparathyroidism** or **parathyroid hormone** anywhere in this guideline as a risk for cardiovascular disease. We appreciate this is not a guideline for hyperparathyroidism or hypercalcemia, but cardiovascular disease is a well-documented risk of hyperparathyroidism and should be added as a risk factor to be considered by health care providers and patients. We are aware that NICE chooses not to acknowledge papers published outside the UK on the basis they do not account for the British population, but if studies are not being conducted in the UK, we feel the British public are placed at unnecessary risk by their absence. The following paper collected data from patients in Amsterdam. We appreciate the much smaller scale of likely participants compared to the UK. Published in The Journal of Clinical Endocrinology & Metabolism, Volume 98, Issue 10, 1 October 2013, Pages E1583–E1590in 2013 entitled **'PTH: A New Target in Arteriosclerosis?'** Context: Growing evidence demonstrates that hyperparathyroidism is associated with an increased risk of cardiovascular morbidity and mortality.	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid modification therapy. No recommendations could therefore be made on risk assessment. However, the recommendations in primary prevention of CVD in NG238 (formerly CG181) include 1.1 Identifying and assessing cardiovascular disease risk for people without established cardiovascular disease. Consideration of a condition such as hyperparathyroidism would form part of the risk assessment.

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				Objective: In this study the relationship of serum PTH levels within the normal range with CVD and abdominal aortic calcifications was investigated. Design: A cross-sectional, population-based study was performed using data of the Longitudinal Aging Study Amsterdam, including 558 men and 537 women, aged 65–88 years. Models were controlled for sex, age, body mass index, hypertension, diabetes mellitus, high-density lipoprotein cholesterol, total cholesterol, smoking, physical activity, alcohol consumption, glomerular filtration rate, season of blood collection, calcium or diuretic use, and serum 25-hydroxyvitamin D and osteocalcin levels when these variables were found to be relevant confounders. Results: Multivariate models showed that subjects in the highest quintile of serum PTH had a significantly higher risk of CVD as compared with subjects in the lowest quintile (odds ratio 2.22, confidence interval 1.39–3.56). The relationship between PTH and abdominal aortic calcifications was observed only in men, which remained significant after adjusting for confounders (odds ratio 4.03, confidence interval 1.50–10.83). Conclusions: This study demonstrated that in older persons the presence of serum PTH levels within the upper normal range is highly related to CVD. In men, this association may partly be explained by calcifications of	

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				the abdominal aorta. Because CVD poses an important health risk, further elucidation of the role of serum PTH in CVD and arteriosclerosis is relevant.	
Hyperparathyroid UK Action4Change	Guideline	006		1.1.10 We would recommend adding a further bullet point to this section: 'Recognise that CVD risk tools may underestimate risk in certain groups of people, including but not limited to: People with primary hyperparathyroidism including those with Parathyroid hormone (PTH) in the upper normal range)	Thank you for your comment. This recommendation was not updated as part of this guideline. However, recommendation 1.1.10 covers risk tools for the people without established cardiovascular disease and covers the underestimation of risk in certain groups.
Hyperparathyroid UK Action4Change	Guideline	007		1.1.16 'Consider using a lifetime risk tool such as QRISK3-lifetime to inform discussions on CVD risk and to motivate lifestyle changes, particularly for people with a 10-year QRISK3 score less than 10%, and people under 40 who have CVD risk factors. [2023] The QRISK3 link updated in 2023, should be updated with priority, to included hyperparathyroidism, hypercalcaemia and parathyroid hormone. We are currently processing data for cardiovascular events throughout the NHS. Whilst it is not yet complete, we have recorded from 72 NHS Trusts; 3,719 heart	Thank you for your comments. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid lowering therapy. The committee were therefore unable to make recommendations on risk assessment.

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				attacks, 3,336 strokes and 70 TIAs, with hypercalcemia between 2019 – 2022. These figures may be a drop in the ocean compared to the total number of cardiac events; 606,869, but PTH was most likely not recorded which increases cardiovascular risk, and very likely not even considered a risk which is what we are recommending. With a total of 606,869 cardiac events recorded at 72 NHS Trusts between 2019 – 2022, we believe it is worthwhile including 'hypercalcemia, hyperparathyroidism and parathyroid hormone' as potential risk factors for cardiovascular disease.	
Hyperparathyroid UK Action4Change	Guideline	007		1.1.14 'Document the discussion relating to the consultation on risk assessment and the person's decision. [2008].' A risk assessment dated 2008, assumes there have been no advances in risk assessment in fifteen years. Surely the 2008 needs to be deleted or replaced with the updated 2023 link? Even though we would recommend that QRISK3 also be updated to include hyperparathyroidism, hypercalcaemia and parathyroid hormone.	Thank you for your comments. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid lowering therapy. The committee were therefore unable to make recommendations on risk assessment.
Hyperparathyroid UK Action4Change	Guideline	023		We would strongly advise to include a recommendation for imperative research on a link to ischemic stroke and parathyroid hormone and/or that NICE change their restrictions on existing studies from outside the UK based on the evidence which is already available but considered	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid lowering therapy. The committee were therefore unable to make the research recommendation

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				for UK patients and the impact on an already struggling NHS. Here is another strong example of risks associated with parathyroid hormone which we feel must be taken into consideration by health care providers. The Journal of Neurology Research in North America published 'The Association Between Hyperparathyroidism and Ischemic Stroke Subtypes' Volume 10, Number 1, February 2020, pages 7-12 Introduction; 'There is a substantial amount of research suggesting that parathormone (PTH) may be involved in the development of subclinical and clinical vascular diseases through mechanisms of endothelial dysfunction, increased vascular stiffness, hypertension, and atherosclerosis. However, although its association with cardiovascular diseases and increased risk of atherosclerosis have been investigated frequently, the number of studies particularly focusing on the association between PTH elevation and stroke, and cerebral atherosclerosis is quite limited. In a crucial study by Sato et al, increased PTH levels were found in female patients with ischemic stroke, and the authors drew attention to the possible relation between hyperparathyroidism and stroke. More recently, Celik et al remarked upon serum PTH level as a potential predictor	suggested. NICE guidelines include all studies meeting the review protocol criteria which can include those conducted outside the UK. See https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission

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				for determination of stroke risk. They also emphasized the need for future studies to investigate the effect of PTH on stroke risk. The determination of the potential importance of the PTH elevation as a risk factor for stroke would certainly contribute substantially to our understanding of the pathophysiology of the unknown aspects of stroke and potentially lead to a large public health implication in this area. Taken together, we aimed to reinvestigate the frequency of PTH elevation in our cohort of patients with ischemic stroke. Remarkably, we focused on its relationship with specific stroke subtypes which was not examined previously. In conclusion, herein, we found a high incidence of hyperparathyroidism in our group of patients with ischemic stroke. A remarkable result was that elevation of PTH was found to be significantly associated with the ischemic stroke subtype of extracranial atherosclerosis. Clarification of these results in the future large-scale studies may provide crucial perspectives regarding our understanding of the pathophysiology of some subtypes of ischemic stroke and potentially lead to a large public health implication in this area.	
Hyperparathyroid UK Action4Change	Guideline	023		'Serum parathyroid hormone levels in patients with chronic right heart failure' is the title of a paper published in December 2019 by the	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of

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				Department of Cardiology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215002, P.R. China, Department of Cardiology. 'Parathyroid hormone (PTH) is a novel cardiovascular biomarker which is particularly useful for detection and assessment of heart failure. A multiple linear regression analysis model was used to evaluate the independent factors of PTH levels in patients with right HF. The results showed that the serum PTH levels in the right HF group were significantly higher compared with the control group. After adjusting for predictors of right HF, serum PTH levels were associated with right HF with an odds ratio of 1.066 (95% confidence interval: 1.030-1.102, P<0.001. Serum PTH levels were independently correlated with plasma N-terminal pro-B-type natriuretic peptide levels, right ventricular end-diastolic diameter and severity of lower extremity oedema (all P<0.05). Therefore, based on the results of the present study, PTH may be a useful biomarker for detection and assessment of right HF. On the basis of this study and others shared in comments submitted by us, we would like to recommend that hyperparathyroidism, hypercalcaemia and parathyroid hormone be added (with some urgency) to this guideline recommendations for research.	lipid lowering therapy. The committee were therefore unable to make the research recommendation suggested.

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Leadgate Surgery	Guideline	General	General	I would like to respond to your consultation on the proposed changes to managing lipids in patients with manifest atherosclerotic cardiovascular disease (ASCVD) in CG181. I am not a lipid specialist. I am general practitioner with significant experience in implementing guidelines. The following information is relevant to this discussion. **Supporting Information** 1. I do not believe the following statement from the consultation is accurate: *The committee noted that a lipid target based on a percentage reduction in non-HDL cholesterol was not practical as current electronic clinical systems are not set up to generate this data. The lack of a baseline figure against which to measure any percentage reduction is a particular problem in secondary prevention as people may start lipid-lowering treatment after an acute event and their lipid level at that time may not be recorded*. My practice has 6050 patients, 6.3% of whom have ASCVD. Of the 93.3% of those patients on lipid lowering therapy (LLT), 93.3% have a non-HDLC lipid target set, based on a 40% reduction from baseline. In addition, 14.5% of the population are taking LLT for primary prevention	Thank you for your comment. The committee's discussion on the limitations of current electronic systems in primary care was based on their own experience and that of the expert witness statement but they acknowledge that the calculation may be possible in some GP surgeries. The calculation is easier in newly presenting patients being managed for the primary prevention of CVD because of the availability of a baseline non-HDL level. Recommendation 1.7.3 is on when to start on a lower dose than Atorvastatin 80mg. There are separate recommendations (1.8.1-1.8.3) on primary and secondary prevention for people with chronic kidney disease in the integrated guideline NG238 (formerly CG181). Recommendations are made based on the expectation that healthcare professionals will prescribe or advise their use within the terms of their UK marketing authorisations, as described in manufacturers' SPCs, and that healthcare professionals should take note of the contraindications, warnings, safety recommendations and any monitoring requirements for the medicine explained in the SPC and the BNF. See Making decisions using NICE guidelines | NICE guidelines | NICE guidance | Our programmes | What we do | About | NICE

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				and 95.0% of those patients have an equivalent non-HDLC target. This was achieved with very simple tools, principally: a simple view to show previous lipid results alongside LLT prescriptions; a prompt to invite the clinician to record a target when starting LLT. Even if your recommendation to move to an absolute non-HDLC target for ASCVD is approved, this will not remove the need for clinicians to be able to calculate 40% reduction in non-HDLC, because this will still be needed for patients receiving LLT for primary prevention, when it is critical to determine need for dose titration. 2. Although the default starting LLT dose in ASCVD is atorvastatin 80mg, there are very many patients for whom this is not suitable. The BNF, CKS and CG181 all give many examples when lower starting doses must be used or should be considered (including age >70y, CKD, HIV meds, concomitant amiodarone, amlodipine, diltiazem, verapamil, ciclosporin, active liver disease, significant alcohol consumption, muscle disorders). In my practice 71.5% of patients with ASCVD have one or more of these conditions (this only includes people with cirrhotic liver	The committee value the information you have provided from your own practice. The target is population based and the committee acknowledge that at the level of the individual it may need to be modified for example based on the individual's risk and recommendation 1.7.11 is aimed at the treatment of people below the target. The committee have made an additional recommendation 1.7.8 to emphasise the importance of shared decision making when deciding whether to escalate treatment. The committee did consider retaining the 40% reduction from baseline (and even 50% as per the ESC guidance) for secondary prevention patients and then the target would be to achieve either an absolute level or the % reduction, whichever produced the lowest LDL-c (or non-HDL-c result). However, whilst this appeared to be scientifically more robust, the pragmatics were such that the committee felt it would produce confusion and (in many cases) might be impossible to implement and therefore and therefore the more simplistic approach was to adopt an absolute value as the threshold for escalation. Although the 40% reduction has been retained for the primary prevention population it is recognised then outside of skilled/high-performing practices such as yours, this "target" is largely ignored. Identifying a cost-effective target for primary prevention was outside of the scope

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				disease not everyone with liver disease – if the latter patients are added it rises to 74.3%). This is a slightly simplistic analysis as some will not have had that risk factor when they developed ASCVD, when the decision to start LLT was taken, but even taking out age as one of the factors, the proportion is still 47.9%. i.e. for a sizeable proportion of patients with ASCVD, careful consideration is needed before initiating atorvastatin 80 as first line treatment and for many it should definitely not be the starting dose. 3. It is important to understand the characteristics of the ASCVD cohort. The age profile of the patients with ASCVD at my practice is shown below. Age range — Patient Count 20-29 — 1 30-39 — 4 40-49 — 10 50-59 — 43 60-69 — 104 70-79 — 110 80-89 — 90	for this update (https://www.nice.org.uk/guidance/gid-ng10368/documents/final-scope-2) so the emphasis was very much on reinforcing the cost-efficacy of statin therapy and the very rates of true side-effects. Thank you for your comments. In regard to comments on the proposed indicator: • The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. • The NICE specification notes that personalised care adjustments could be used to exclude patients from indicator denominators dependent on individual circumstances. Examples of these are included in the indicator specification and have been amended following this consultation. • Non-haemorrhagic stroke is not included in the NICE indicator specification. • The indicator has been amended to align with NG238 (formerly CG181). The construction now searches for LDL first, and if not found, non-HDL. • The current NICE menu indicator NM212 measures the percentage of patients with cardiovascular disease who are currently treated with a lipid lowering therapy. This

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				18 57% are of the patients are aged 70 or over and 28% are aged 80+. Patients in primary care tend to be, on average, older than patients in the clinical trials of high intensity LLTs. Looking at the published exclusion criteria for the ORION inclisiran trials, using a very simple search, at least 19% of my ASCVD patients would definitely have been excluded from that trial and many more would almost certainly have been excluded. Some other important comorbidities are shown in the table below: Comorbidity | Palliative care register | 7.3% Severe frailty | 2.1% Moderate or severe frailty | 11% Palliative care or moderate/severe frailty | 13.6% CKD 3-5 | 24.6% CKD 3-5 (higher risk) G3aA3, G3bA2/3, G4/5 | 9.2% 4. The following data relates to patients with ASCVD registered with my practice. Of the patients with a 40% reduction non-HDLC target, only 37.9% have a target non-HDLC <=2.6, so moving to a blanket target of <=2.6 would lead to the majority of ASCVD patients having a tighter target than the existing guideline.	includes statin and non-statin therapies. Previous indicator work in this area suggests that intensity of statin therapy is not extractable using GPES. We will continue to explore potential new indicators relevant to other aspects of the lipid management pathway.

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				Of the patients with a 40% reduction non-HDLC target greater than 2.6, 49.7% of patients are already achieving non-HDLC <=2.6, i.e. the change to the guideline would have no impact to these patients who are on established treatment. Of the patients with a 40% reduction non-HDLC target greater than 2.6, who have not already achieved non-HDLC <=2.6, 66% are achieving their 40% reduction target. These are the patients who are achieving the existing target but are not achieving the proposed target – this represents ~21% of all the ASCVD patients at my practice who have a recorded target non-HDLC. Of these patients, many have relatively low LDL-C levels (distribution shown below). It is likely these some of these patients have adequate lipid control despite a non-HDLC >2.6 – intensifying treatment in these patients to satisfy the nonHDLC<=2.6 might be inappropriate. Very few patients have an LDLC>=2.6 (the threshold for inclisiran). This contrasts with the patients who have not achieved their 40% reduction target where LDLC levels are much higher (distribution shown below).	

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				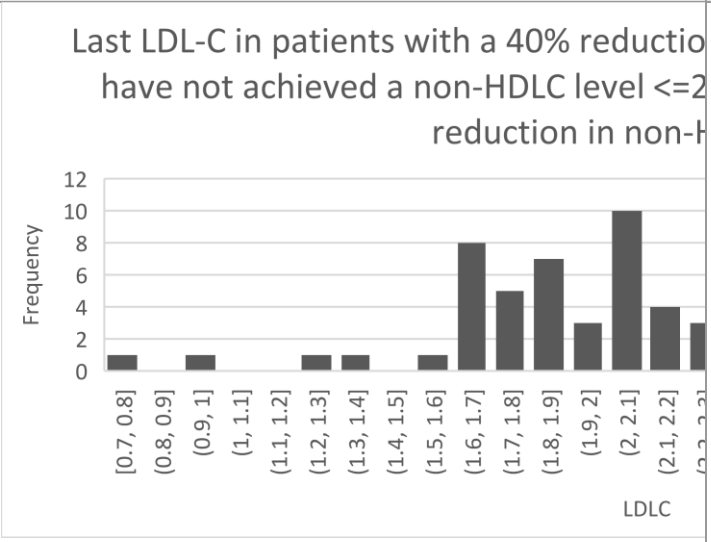	

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				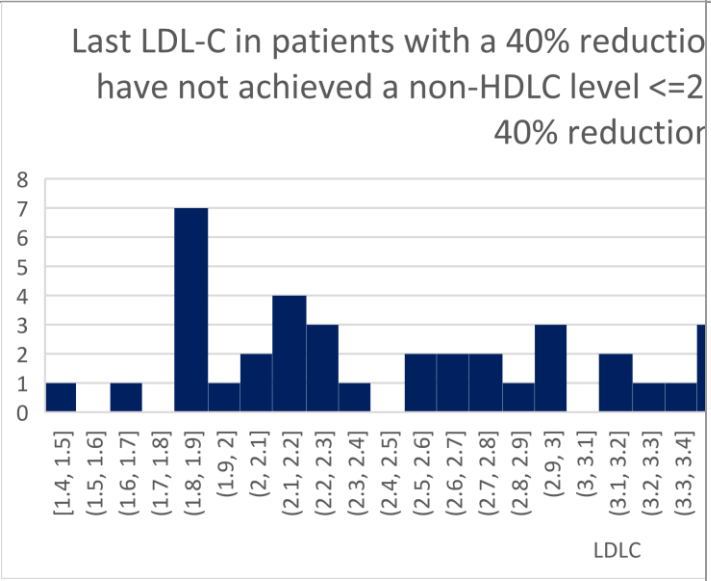 **Implications** 1. **Undertreatment** The proposed guidance risks potential undertreatment for some patients. A significant number of patients have a target non-HDLC lower than 2.6 under the current guidance, e.g. 11% of ASCVD patients at my practice with a target non-HDL cholesterol have a target <=2.2. Some of	

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				these patients might be 'undertreated' under the proposed guidelines if they just achieve the <=2.6 threshold. This is more likely for people who aren't initiated on very high intensity statin (see point 2.) with the risk that lower intensity LLT is started but not escalated once the patient achieves the <=2.6 target. There is also a risk that this could lead to loss of utility of the target for detecting non-concordance: failure to achieve a 40% reduction with HIST is strongly suggestive of poor concordance, but if the 40% reduction target is significantly lower than 2.6, then the patient might achieve nonHDLC <=2.6 whilst poorly concordant with LLT. In addition, many patients currently taking lower intensity LLT will have achieved a non-HDLC <=2.6 so the proposed new target will imply those patients do not need LLT intensification (or at least fail to provide incentivisation for this), when many should be offered higher intensity LLT. 2. **Overtreatment** The blanket approach of the <=2.6 target could potentially lead to some patients being inappropriately targeted for very intensive treatment, even though they might have already achieved a significant reduction in cholesterol. From point 3. above, it can be seen that a	

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				significant proportion of these patients have significant comorbidity associarted with a significant reduction in lifespan or increased risk of adverse reactions to LLT – both situations where the risks/costs of very high intensity LLT are likely to outweigh the benefits, both for the patient and healthcare system. **3. Unachievable Target** There will be a significant number of patients where the proposed target is unachievable. These will be patients taking the maximum tolerated dose of statin combined with ezetimibe (or ezetimibe/bempedoic acid) who have not achieved non-HDLC <=2.6 despite good concordance with treatment, even though the majority will have achieved a 40% reduction in non-HDLC. For the majority of these patients there will not be any other treatment options, or further treatment may well be unnecessary, for the following reasons: a. The patient has a low or very low LDL-cholesterol b. The patient has an LDL-C below the threshold for inclisiran/PCSK9i treatment – see the graph in point 4. above showing the majority of these patients are below the threshold for those treatments	

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				c. Even with a high LDLC, the patient is ineligible for inclisiran/PCSK9i – mainly this is patients with angina without ACS/MI, or patients with TIA(s) but not stroke, both situations where inclisiran is not recommended. This means that at every annual review the patient will 'fail' and there will be upset for the patient and the opportunity cost of the clinician trying to understand what should be done, when nothing further can be done. **QOF Indicator** The current CHOL002 indicator (nonHDLC <2.5 for all CVD including non-atherosclerotic CVD) is one of the most unusual QoF indicators for the following reasons: • For individual patients, the indicator does not measure the care which accompanying notes to the indicator suggest should be delivered. The notes point to the AAC guidance which recommends default atorvastatin 80mg aiming for a 40% reduction in non-HDLC, with consideration of addition of ezetimibe if not achieved, or, inclisiran/PCSK9i if certain LDLC thresholds are not met.	

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				• The current denominator includes some people who do not have ASCVD e.g. patients with haemorrhagic stroke or type 2 myocardial infarctions. • The indicator has very low achievement thresholds, with the implication given that only a small proportion of patients are expected to achieve the indicator. • The way the indicator is structured can be confusing to understand. The business rules structure means that practices with laboratories which report nonHDLC will never achieve the indicator based on the LDLC result. It does however give a perverse incentive to delete nonHDLC results in patients who do not achieve nonHDLC <2.5 but do achieve LDLC <1.8 (see point 4). It would be much better to explain that the indicator detects: *……...for laboratories which report non-HDLC, patients who have a recording of non-HDL cholesterol in the preceding 12 months that is lower than 2.5 mmol/L, or where laboratories do not report non-HDL cholesterol, a recording of LDL cholesterol in the preceding 12 months that is lower than 1.8 mmol/L.* I don't imagine there are many laboratories	

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				which don't report nonHDLC, if there are, perhaps NHSE should mandate that they do. • This indicator does not have any exclusion clauses which is very odd and out of line with virtually all other QoF indicators. • Unlike all other QoF indicators, continually increasing 'performance' will not equate to continually improving patient care. For all other QoF indicators, achieving high performance involves delivering appropriate care, offering care which is declined or identifying that the care is inappropriate for that patient. For CHOL002, maximum 'performance' could only be achieved by delivering inappropriate care e.g. providing high intensity LLT to terminally ill patients or forcing patients to have treatment against their will/best interests. • Taken together, the points above show that CHOL002 is really a population level indicator which is being inappropriately used in a system which is designed for use at the individual level. **Recommendations for Future Indicator**	

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				• The new indicator should align with whatever recommendations are made in the NICE guideline .e.g. only use an indicator requiring non-HDLC <=2.6 if that is the recommendation in the guideline. If it is decided to stick with a 40% reduction target, do not use an absolute target in the indicator. Alternative options in that case would be: o Two indicators ▪ Proportion of people with ASCVD with a recorded target non-HDLC ▪ Proportion of people achieving that target o An indicator looking at the proportion of people on very high intensity LLT (i.e. those doses expected to deliver a 50% reduction in non-HDLC) e.g. ▪ Atorvastatin 80mg ▪ Rosuvastatin 40mg ▪ Atorvastatin/rosuvastatin + ezetimibe ▪ Simvastatin >=20mg + ezetimibe ▪ Inclisiran ▪ PCSK9i • The new indicator must exclude people without ASCVD e.g. who have only had a haemorrhagic stroke or people who have only had a type 2 myocardial infarction.	

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				• The new indicator must be structured so that an improvement in performance always means that more appropriate care is being delivered. This must allow for the following exclusions: ○ LLT not indicated – e.g. terminally ill people or those with significant frailty or comorbidity which indicates a very significant reduction in life expectancy ○ LLT declined – to allow for patient choice ○ Patient on maximally tolerated LLT ▪ This is needed to cover patients who are willing to have/able to tolerate lower potency LLT treatment but not higher potency ▪ This would also cover the 'limbo' patients who are on maximum tolerated doses of (usually) statin and ezetimibe, who are not achieving a target lipid level but who are not eligible for additional therapies such as inclisiran/PCSK9i ○ Adverse reactions and allergies are more difficult for this indicator. For patients with an LDLC <2.6 (or angina without ACS/TIA without stroke), recorded ADRs to statins and ezetimibe should except the patient. For patients with an LDLC >2.6, they	

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				would also need an ADR to inclisiran and patients with higher LDLC results (level depending on the nature of their ASCVD) would also need a ADR to PCKS9i ○ Combinations of exceptions would also be needed. E.g. For patients with an LDLC <2.6 (or angina without ACS/TIA without stroke), they might be appropriately excepted if they decline a statin and have an adverse reaction to ezetimibe. • The new indicator should have the same overall opt-out options as other indicators e.g. patient has chosen not to receive lipid optimisation care • The new indicator should have the same procedural exceptions e.g. the patient has been invited for lipid optimisation on several occasion but not attended. • The wording of the indicator should be clearer that whether or not it depends on non-HDLC or LDLC results depends on the local laboratory. Consideration should be given to ensuring that all laboratories report non-HDLC which is an incredibly easy adjustment to make as this is only a calculated result from existing tests. The indicator could then be changed to only a non-HDLC target, unless expert guidance indicates that LDLC levels are useful e.g. indicator is	

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				achieved if the last lipid result contains a non-HDLC <=2.6 OR, if this is not achieved, the last lipid result contains an LDLC <=2 I would be grateful if this information could be taken into consideration when considering your update to CG181 and the proposed new performance indicator.	
Milton Keynes University Hospital	Guideline	005	007	NICE target for LDL of 2 mmol/L and non-HDL of 2.6 is out of step with UK guidelines (NHSE/ACC lipid pathway, recent QOF target, 2023 National Stroke Guideline, AHSN lipid pathway for ACS and stroke, JBS3), European Guidelines (ESC, EAS) and US Guidelines (AHA, ACC). We have been teaching GPs and other doctors about LDL target of 1.8 and non-HDL 2.5. This new target of LDL of 2 would only confuse users.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. Cost effectiveness has not been considered by other guidelines. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024.

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					Recommendation 1.7.11 recommends that ezetimibe can be considered to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is achieved.
NHS England	Guideline	005	005	We welcome the inclusion of a clear non-HDL cholesterol target (and equivalent LDL target) which will simplify management of lipids in primary care.	Thank you for your comment.
NHS England	Guideline	005	008	This seems to refer to all people, it may be clearer to say 'Statins for all people (including those who have diabetes)'.	Thank you for comment. The heading has been written in accordance with NICE style.
NHS England	Guideline	006	004 – 025	Nothing in these recommendations refers to shared decision making and patients choice of treatment.	Thank you for your comment. The committee have made a new recommendation 1.7.8 recommending that there should be a discussion between the clinician and the person when deciding whether to escalate treatment. Recommendation 1.11.11 has been edited to include sharing decision making. This guideline will also cross refer to the NICE guideline on shared decision making Shared decision making (nice.org.uk)
NHS England	Guideline	006	004 – 025	There is a gap in the recommendations as there is not an option to not have any statin. This may be one option for the patient depending on their own circumstances, clinical condition, values and preferences.	Thank you for your comment. The word offer is used in the recommendations to enable the person to choose whether to take a statin or not as part of shared decision making with the clinician. This guidelines also cross refers to the NICE guideline on patient experience Overview | Patient experience in adult NHS services: improving the experience of care for people using adult NHS services | Guidance | NICE which

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					makes recommendations on enabling patients to actively participate in their care.
NHS England	Guideline	006	004 – 025	All recommendations in this section should make reference to having a conversation with the patient to check adherence before adding in more treatments.	Thank you for your comment. Recommendation 1.9.1 refers to adherence if the lipid target is not reached. This guideline also cross-refers to the NICE guideline on medicines adherence (CG76).
NHS England	Guideline	006	005	It would be helpful to know after what time period of taking the statin the target should be re-checked? (this could cross-reference with 1.6.4).	Thank you for your comment. Recommendation 1.11.1 specifies when to monitor response to treatment.
NHS England	Guideline	006	007	We suggest putting 'optimise adherence to diet and lifestyle measures' as the first bullet.	Thank you for your comment. The bullets points are in no specific order and the committee agreed that it was important to follow all of the bullet points.
NHS England	Guideline	006	007	Atorvastatin doesn't have to be taken at night so timing isn't relevant.	Thank you for your comment. The evidence for this recommendation was not reviewed as part of this update and therefore only minor wording changes could be made by the committee.
NHS England	Guideline	006	009	Does this recommendation assume that the only statin a person is prescribed is atorvastatin? We suggest amending the text to "consider increasing the atorvastatin dose if started on less than atorvastatin 80mg and the person…"	Thank you for your comment. The evidence for this recommendation was not reviewed as part of this update and the committee were therefore only able to make minor wording changes.
NHS England	Guideline	006	013 – 014	This recommendation is not very shared-decision focused. Please review the language so it takes into account a person's values and preferences in deciding the options for them. Instead of saying 'try the following	Thank you for your comment. We have edited the recommendation as suggested.

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				strategies' suggest 'discuss with the patient the following strategies'.	
NHS England	Guideline	006	013 – 029	Should there also be an option to completely stop the statin (after a shared decision-making conversation) in this section?	Thank you for your comment. Recommendation 1.11.11now refers to shared decision making and cross refers to the NICE guideline on multimorbidity (NG56) for recommendation on reviewing medicines, including reducing and stopping medicines.
NHS England	Guideline	006	018 – 019	'Group' may not be the right term here, suggest 'reducing the dose of a high-intensity statin' (line 18) and 'changing the stating to a lower intensity group' to 'consider a lower intensity statin' (line 19)	Thank you for your comment. The edits you suggest have been made to recommendation 1.9.2.
NHS England	Guideline	006	027	We welcome the clear recommendation to offer ezetimibe to statin if target levels are not achieved.	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
NHS England	Guideline	006	027	Recommendations regarding use of ezetimibe does not correlate with the recommendations under 1.6.11 (page 7 line 005).	Thank you for your comment. Recommendation 1.6.9 has been deleted.

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NHS England	Guideline	006	027 – 029	It would be helpful if a timeline is given for 'achievement' of the target (i.e., when to re-check lipids)	Thank you for your comment. Recommendation 1.11.1 covers when to re-check lipids.
NHS England	Guideline	007	001	It is good to include recommendations for escalation of treatment to consider alirobumab… However, pathways for such referrals and treatment from primary care are not fully established and might need further considerations about budgetary and practical arrangements.	Thank you for your comment.
NHS England	Guideline	007	001	The current wording suggests that all three treatments should be used together. This is not the case, so we suggest changing the wording to reflect this.	Thank you for your comment. We have edited this recommendation and now refer to the technology appraisals instead.
NHS England	Guideline	007	001	We welcome the clear recommendation to consider intensification of therapy with alirocumab, evolocumab or inclisiran, in line with their respective TAs, where lipid levels are not achieved.	Thank you for your comment.
NHS England	Guideline	007	005	The recommendation to consider adding ezetimibe to statin therapy, even if the treatment target is achieved is likely to confuse clinicians – on what basis should they make that decision? This recommendation could apply to all people – under which circumstances or which patient groups should the addition of ezetimibe be considered?	Thank you for your comment. We have edited recommendation 1.7.11 to make it clear that ezetimibe could be considered to reduce CVD risk further. This would depend on several factors and would be discussed as part of shared decision making with the person.
NHS England	Guideline	007	005	Recommendation "to start ezetimibe in addition to maximum tolerated intensity and dose of statin even if lipid targets of secondary prevention of CVD is achieved"	Thank you for your comment. We have edited recommendation 1.7.11 to make it clear that ezetimibe should be considered to reduce CVD risk further. This

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				needs further clarification as it can imply that all patients should be started on ezetimibe.	would depend on several factors and would be discussed as part of shared decision making with the person.
NHS England	Guideline	007	009	We welcome the clear recommendation to use ezetimibe first line where patients cannot tolerate statin therapy.	Thank you for your comment.
NHS England	Guideline	007	014	We suggest putting the TAs in alphabetical order as in the wording of the recommendation.	Thank you for your comment. The TAs in recommendation 1.10.2 are now listed in alphabetic order.
NHS England	Guideline	007	014	We welcome the clear recommendation that in cases of statin intolerance, where ezetimibe fails to achieve treatment targets. alirocumab, bempedoic acid, evolocumab and inclisiran can be considered in line with their respective technology appraisals.	Thank you for your comment.
NHS England	Guideline	007	020 - 023	Recommendation for monitoring post treatment could be brought in line with recommendations by BNF as it highlights some exceptions where earlier monitoring may be indicated. Moreover, it may be useful to include indications for monitoring CK and renal function in some cases.	Thank you for your comment. Recommendation 1.11.1 now recommends at 2 to 3 months which is appropriate for the majority of people but does not preclude an earlier blood test based on the individual. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid modification therapy. The committee therefore focused their recommendations on monitoring specific to the escalation of lipid lowering treatments.

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NHS England	Guideline	007	020 - 023	We would expect these measurements should be carried out before starting treatment (see BNF monitoring requirements of statins).	The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid modification therapy. The committee therefore focused their recommendations on monitoring specific to the escalation of lipid lowering treatments.
NHS England	Guideline	007	024 - 029	We recommend adding a bullet point to cover checking adherence and a shared decision-making conversation about whether the treatment is still appropriate or not for the patient.	Thank you for your comment. Recommendation 1.11.11has been edited to refer to shared-decision making regarding whether to continue lipid lowering treatment. It also cross-refers to the guidelines on multimorbidity which makes recommendations on whether to discontinue treatments.
NHS England	Guideline	008	002 - 007	We recommend adding an explanation of what a 'low intensity statin' is to the 'terms used in the guidance' section.	Thank you for your comment. A definition of a low intensity statin has been added to the guideline.
NHS England	Guideline	013	023	We welcome a clear, evidence based proposed NICE indicator which takes into account cost-effectiveness with a non-HDL cholesterol target of 2.6 mmol/litre.	Thank you for your comment.
NHS England	Guideline	General	General	The title of the guidance could be more specified to reflect that it is most relevant to secondary prevention of CVD.	Thank you for your comment. The recommendations on secondary prevention have now been integrated with those on primary prevention. The title of the guideline as a whole is Cardiovascular disease: risk assessment and reduction, including lipid modification.

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NHS England	Guideline	General	General	Please note recent LeDeR research: kcl.ac.uk/ioppn/assets/fans-dept/leder-main-report-hyperlinked.pdf	Thank you for sharing this information.
NHS England	Guideline	General	General	We recommend including reference to the importance of Communication: Using simple, clear language, avoiding medical terms and 'jargon' wherever possible. Some people may be non-verbal and unable to describe verbally how they feel. Pictures may be a useful way of communicating with some people, but not all.	Thank you for your comment. The committee agree the way people are communicated with is important and that they should be offered information in an appropriate format. These recommendations form part of the guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification. This guideline cross-refers to the NICE guideline on patient experience (CG138), which makes recommendations on Enabling patients to actively participate in their care (section 1.5).
NHS England	Guideline	General	General	We strongly suggest the document makes reference to making reasonable adjustments. This is a legal requirement as stated in the Equality Act 2010. Adjustments aim to remove barriers, do things in a different way, or to provide something additional to enable a person to receive the assessment and treatment they need. Possible examples include; allocating a clinician by gender, taking blood samples by thumb prick rather than needle, providing a quiet space to see the patient away from excess noise and activity.	Thank you for your comment. Making reasonable adjustments as required by the Equality Act is a statutory requirement and so this requirement is not repeated in each individual NICE guideline.

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				We recommend including reference to the Reasonable Adjustment Digital Flag (RADF) and the RADF Information Standard which mandates all providers and commissioners of health services and publicly funded social care to identify, record, flag, share, meet and review Reasonable Adjustments, including details of their underlying conditions. DAPB4019: Reasonable Adjustment Digital Flag - NHS Digital	
NHS England	Guideline	General	General	In addition to targets in the guideline, we would welcome more focus on supportive interventions such as diet and lifestyle, with emphasis on shared decision-making discussions with patients (i.e. cross referring from the treatment section to lifestyle changes and this should be reiterated in the pharmacological treatment sections).	Thank you for your comment. The committee agree and have now edited the recommendations to emphasise shared decision making and diet and lifestyle changes. A new recommendation, 1.7.8, refers to a shared decision between the clinician and the person whether to escalate lipid-lowering treatment. Recommendation 1.7.4 refers to diet and lifestyle changes. Recommendation 1.11.11 refers to shared decision making and diet and lifestyle changes.
NHS England	Guideline	General	General	Recommendation 3 of the National Overprescribing Review is: In developing and updating guidelines, NICE and professional bodies should include recommendations for reviewing and discontinuing medicines, where appropriate, and in the context of shared decision-making supported by decision aids.	Thank you for your comment. The committee agree that reviewing and discontinuing medications is important. The recommendation on the annual medication review has been expanded to encourage a more patient-centred discussion, and cross refers to the guideline on multimorbidity which makes recommendations on this. Also, these recommendations have been integrated with those on

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				There should be a recommendation outlining that if the person at any point no longer wishes to take the statin or it is no longer suitable or relevant for them (e.g. patient approaching end-of-life and/or not wishing to prolong their life or avoid a cardiovascular event) that they have the option for it to be deprescribed.	primary prevention in the guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification. This guideline cross-refers to the NICE guidelines on patient experience (CG138) and shared decision making (NG197) which make recommendations on, for example, valuing people's preferences (recommendation 1.2.13 NG197).
NHS England	Guideline	General	General	This guidance will have a significant impact in terms of the need to align policy including QOF thresholds. Time should be taken to consider what comms will be required across the system to facilitate implementation.	Thank you for your comment. NICE's implementation support and communications colleagues are working with external partners (including NHSE) to consider targeted and clear comms for this update.
NHS England	Guideline	General	General	It would be helpful to include a treatment algorithm in the final guideline to summarise the positioning of the individual lipid lowering options, including the relevant inclusion criteria.	Thank you for your comment. The recommendations have been edited to make it clear that all of the relevant treatment options should be considered, in people above the target, in accordance with the NICE technology appraisals. An algorithm was not therefore thought to be helpful in explaining the recommendations of this guideline.
Nottingham and Nottinghamshire ICB	Guideline	005	005	Rec 1.6.1 target recommendations do not align with QOF target, please could there be consistency	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 (QoF) compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions

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					of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator.
Nottingham and Nottinghamshire ICB	Guideline	006	016	Provide advice on starting dose of rosuvastatin as not licensed for secondary prevention	Thank you for your comment. The evidence for this recommendation was not reviewed as part of this update and the committee were therefore only able to make minor wording changes. We will pass your comment to the NICE surveillance team which monitor key events relevant to the guideline for consideration if the guideline is updated.
Nottingham and Nottinghamshire ICB	Guideline	007	001	Rec 1.6.10 – if ezetimibe is added but patient still has not reached target then they may not be eligible for other treatment options, but still won't be at target. Evolocumab TA is only recommended for those with non familial hypercholesterolaemia and high risk CVD if LDL-C above 4, whilst inclisiran is only an option if LDL-C above 2.6mmol/l. What happens to the patients who are between <2.6mmol but above 2mmol?	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs. Enabling the flexible prescribing of treatments (but in accordance with the TAs) should reduce the number of people who are above the target in this guideline but below that in the TAs.

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Nottingham and Nottinghamshire ICB	Guideline	007	028	Consider non-fasting blood test to inform discussion – please clarify if fasting blood test required before initiation of PCSK9i and inclisiran etc as per the current guidelines https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/	Thank you for your comment. Recommendation 1.11.9 has been edited and now recommends a full lipid profile which could be non-fasted or fasted.
Perspectum	Guideline	General	General	In clinical practice, combined heart and liver dysfunctions coexist in the setting of the main heart and liver diseases because of complex cardiohepatic interactions (Hadi et al, 2020). It is becoming increasingly crucial to identify these interactions between heart and liver to ensure an effective management of patients with heart or liver disease to provide an improvement in overall prognosis and therapy (Hadi et al, 2020). Obesity related liver disease is a major cause of liver failure (Ahn & Sundaram, 2019) (Schiavo, et al., 2018) (Ioannou, et al., 2003) and a modifiable risk factor for cardiovascular disease (Roca-Fernandez, et al., 2023). Indeed, as obesity related liver disease is now better understood, there is a paradigm shift in management, nomenclature, diagnostic criteria, and therapeutic approaches towards metabolic associated liver disease, or steatohepatitis, which have been spearheaded by global	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid modification therapy. The guideline committee was therefore unable to make recommendations on the association between liver and cardiovascular disease.

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				experts in the field (Rinella, et al., 2023). Metabolic dysfunction-Associated Fatty Liver Disease (MAFLD) now focuses on the bidirectional interplay between fatty liver and metabolic alterations (Rinella, et al., 2023) (Pipitone, et al., 2023). In the presence of hepatic steatosis, the MAFLD/MASLD diagnostic criteria (for both adults and children) focus on the finding of any of: a cardiometabolic risk factor using a combination of body measurements (BMI, waist circumference), clinical and health measurements (blood pressure, treatment, type 2 diabetes status) and biochemical markers (fasting serum glucose, HbA1c, plasma triglycerides, cholesterol levels) (Rinella, et al., 2023). **Since MAFLD is a modifiable risk factor for cardiovascular disease would NICE agree there is a clinical need to assess the health of the liver in the management of cardiovascular risk and lipid lowering therapy?** Non-invasive technologies, like **LiverMultiScan**, provide a safe and effective approach to the assessment of liver health. LiverMultiScan is a DTAC-approved MRI-based digital assessment tool which can be easily accessed across the UK in community diagnostic centres (CDCs) and provides the best assessment of key liver characteristics pertaining to MAFLD (liver fat and disease activity. LiverMultiScan's proprietary biomarker, cT1, correlates	

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				with histology (Andersson, et al., 2022) (Banerjee, et al., 2014) and predicts liver- and cardiac-related clinical outcomes (Jayaswal, et al., 2020) (Roca-Fernandez, et al., 2023). Specially relating to cardiovascular (CV) outcomes, cT1 has been shown to be an independent predictor of hospitalisation from CV disease and all cause mortality, even in those without prior history of CVD or chronic liver disease. In fact, established markers of liver fibrosis (FIB-4 index and AST/ALT ratio) were not association with CVD outcomes indicating cT1's superiority in risk stratifying in those earlier in the disease course (Roca-Fernandez et al, 2023). cT1 is also effective at monitoring response to intervention including bariatric surgery (Tan et al, 2023), low energy diets (Koutoukidis, 2023), and in experimental compounds targeting liver specific fat reduction (Harrison et al, 2021), liver lipid reduction (Loomba et al, 2023) and anti-fibrotic therapies (Harrison et al, 2020; Ratziu et al, 2023). It is also the only liver test that can accurately be used to monitor patients' response to treatment (including obesity medications) due to its best-in-class repeatability, reproducibility, coefficient of variation as shown by its use in multiple clinical trials. Most importantly, LiverMultiScan can also be incorporated into patient management as it can serve as a motivational tool for adherence to lifestyle intervention with a visual report that has been shown to improve patients' understanding of their liver disease (McKay, et al., 2021)	

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				presented in a patient-friendly format, unlike all other liver tests. This latter point should not be underestimated. There are serious problems in the UK with health literacy, access and outcomes, all of which are linked; the easier information is to digest for patients, the more likely they are to understand and therefore adhere to treatment course, especially for non-communicable diseases that often can show few symptoms until advanced disease occurs. **References** • Ahn, J. & Sundaram, V., 2019. Obesity and Liver Decompensation. Clin Liver Dis (Hoboken), pp. 12-15. doi: 10.1002/cld.807. • Andersson, A. et al., 2022. Clinical Utility of Magnetic Resonance Imaging Biomarkers for Identifying Nonalcoholic Steatohepatitis Patients at High Risk of Progression: A Multicenter Pooled Data and Meta-Analysis.. Clin Gastroenterol Hepatol., pp. 2451-2461.e3. doi: 10.1016/j.cgh.2021.09.041.. • Banerjee, R. et al., 2014. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. Journal of Hepatology, 60(1), pp. 69-77. • Chen, J. et al., 2011. Early detection of nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease by using MR	

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				nomenclature.. J Hepatol, pp. 00418-X. doi: 10.1016/j.jhep.2023.06.003. • Roca-Fernandez, A. et al., 2023. Liver disease is a significant risk factor for cardiovascular outcomes - A UK Biobank study.. J Hepatol, pp. 00420-8. doi: 10.1016/j.jhep.2023.05.046.. • Schiavo, L. et al., 2018. Nutritional issues in patients with obesity and cirrhosis.. World J Gastroenterol., pp. 3330-3346. doi: 10.3748/wjg.v24.i30.3330. • Tan, H.C., Shumbayawonda, E., Beyer, C., Cheng, L.T.E., Low, A., Lim, C.H., Eng, A., Chan, W.H., Lee, P.C., Tay, M.F. and Kin, S., 2023. Multiparametric Magnetic Resonance Imaging and Magnetic Resonance Elastography to Evaluate the Early Effects of Bariatric Surgery on Nonalcoholic Fatty Liver Disease. International Journal of Biomedical Imaging, 2023.	
PrescQIPP CIC	Economic review	009	013 - 019	Both of the available PCSK9 inhibitors, alirocumab and evolocumab, are included in the primary care drug tariff and therefore could be prescribed in primary care if agreed locally. They remain the most expensive option at present, but systems should be allowed the latitude to agree a local pathway which offers both the best clinical care and the best value from medicines for their locality, and should not be constrained by definitive recommendations regarding choice of injectable unless	Thank you for your comment. We agree that local pathways may differ. We have recommended a treatment target and have not recommended a specific treatment sequence.

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				the balance of outcome evidence overwhelming favours one drug over another. PCSK9i also have more outcome data and can be self-administered by patients reducing the need for additional appointment times.	
PrescQIPP CIC	Economic review	General	General	Current inclisiran contract prices are due to be reviewed by July 2024 and may end in August 2024 and therefore the economic model could be invalid as it is based on the assumption that inclisiran will remain available at the CAA price	Thank you for your comment. The results of the model are dependent on the contract price for inclisiran. We expect that the current discount will be extended. If that is not the case, then the target might have to be re-evaluated.
PrescQIPP CIC	Economic review	General	General	Forecasting of capacity may be inadequate, and the economic model does not include the likely additional local investment required to address Local Medical Committee concerns regarding the administration of inclisiran, and to ensure that prescribing and administration of injectable therapies can take place in primary care. This may render the economic model invalid.	Thank you for your comment. The economic model includes the costs of administration of inclisiran and is valid. A resource impact report and tool will be available when this guideline update is published.
PrescQIPP CIC	Economic review	General	General	Information on predicted number of patients per 100,000 population who are likely to require escalation to injectable therapies is needed to enable ICBs to develop services to support adoption of the guideline.	Thank you for your comment. Table 34 indicates the proportion of people with CVD and on a statin that would need to be escalated at a target of 2.0 mmol/litre LDL-C. A resource impact report and tool will be available when this guideline update is published. This will include estimates of the number of patients that would require escalation to injectable therapies and the associated capacity impact.

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PrescQIPP CIC	Guideline	005	004 – 007	1.6.1 The change from a percentage target to defined absolute target is likely to result in more patients requiring injectable therapies. We are aware that there are currently capacity issues for prescribing and administration of injectable therapies in both specialist lipid services and in primary care. This has resulted in variation in patient access to these treatments and inequity. Additional patient numbers need to be quantified, and the additional costs associated with increasing service capacity to deliver injectable therapies need to be acknowledged and fully taken into account.	Thank you for your comment. Increased uptake of statins, ezetimibe and other lipid-lowering treatments will result in higher medication and monitoring costs to the NHS. It will also contribute to increased workload burden in primary care GP practices and pharmacies and in laboratories processing monitoring tests. The committee agreed this increase is necessary for downstream improvements in population health and the extra cost of lipid-lowering treatment would be partly offset by savings due to a reduction in CVD events (including admissions for stroke or heart disease and cardiovascular procedures).
PrescQIPP CIC	Guideline	005	004 – 007	1.6.1 We support the use of non-HDL-C and the change to a defined target rather than a percentage reduction, as this will simplify monitoring for patients and clinicians. The recommended target levels for non-HDL-C and LDL-C are different to those introduced into the QOF in 2023/4 (CHOL 002) and this may cause confusion in primary care. We agree that the indicator should be amended to align if these targets are agreed. The targets are also different to The Joint British Societies recommendations for a non-HDL cholesterol target of less than 2.5mmol/litre (or LDL cholesterol of less than 1.8mmol/litre) in secondary prevention, which are the same as the current QOF targets.	Thank you for your comment. As you acknowledge, the target in this guideline is based on both clinical and cost effectiveness. This is to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator.

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				We do appreciate that NICE acknowledge this in discussion and that unlike other targets, it is explicitly based on the cost effectiveness of treatment escalation.	
PrescQIPP CIC	Guideline	005	010	1.6.2 We strongly support the use of the wording "offer atorvastatin 80mg" as opposed to "start atorvastatin 80mg" to encourage shared decision making.	Thank you for your comment.
PrescQIPP CIC	Guideline	006	General	We support the approach to optimise therapy with statins followed by addition of ezetimibe prior to further step up to injectable therapies.	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to avoid any potential conflict with the relevant NICE technology appraisals and to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
PrescQIPP CIC	Guideline	007	001 – 004	Further work is needed to ensure full availability of choice to patients either by increasing secondary care capacity or securing agreement locally for prescribing of PCSK9i (and inclisiran in some localities) in primary care.	Thank you for your comment.
PrescQIPP CIC	Guideline	007	001 – 004	Guidance is needed on the sequential use of injectable therapies e.g. if a patient has failed to respond to therapy with inclisiran, should they be offered a trial of a PCSK9i?	Thank you for your comment. The scope of this guideline update was to produce a target and not a treatment pathway and we have therefore referred to the relevant technology appraisals in recommendation 1.7.10.

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PrescQIPP CIC	Guideline	007	001 – 004	The guideline should include stopping criteria for injectable therapies i.e. no change in non HDL (which indicates non-compliance with self-injecting for PCSK9i or non-attendance for inclisiran appointments).	Thank you for your comment. Recommendation 1.7.9 cross-refers to the recommendations in the NICE guideline on multimorbidity (NG56) on reducing or stopping medicines. The guideline also cross-refers to the NICE guideline on medicine adherence (CG76) which makes recommendations on reviewing medicines including adherence.
PrescQIPP CIC	Guideline	007	001 – 004	1.6.10 The current wording "If the lipid target for secondary prevention of CVD is not achieved (see recommendation 1.6.1), consider alirocumab, evolocumab and inclisiran" should be amended to read ""If the lipid target for secondary prevention of CVD is not achieved (see recommendation 1.6.1), consider alirocumab **or** evolocumab **or** inclisiran". The current wording implies that all these agents might be considered in combination. It should be made clear that PCSK9 inhibitors and inclisiran should not be prescribed concurrently.	Thank you for your comment. Recommendation 1.7.10 has been edited to refer to the technology appraisals rather than listing the treatments.
PrescQIPP CIC	Guideline	007	005 - 007	1.6.11 In isolation this recommendation does not appear logical. We believe that the rationale for this needs to be included in the guideline, or the recommendation removed. The purpose of the guideline update is to provide the targets for secondary prevention. Why would there be a recommendation to add another drug if the target is already achieved? The committee acknowledges that "recommending ezetimibe to people at lower levels of cholesterol might	Thank you for your comment. The evidence showed (see evidence review D) that ezetimibe was cost effective regardless of the person's lipid levels, the committee therefore decided that it could be considered for people with lipid levels below the agreed targets of 2.0 mmol/litre for LDL cholesterol and 2.6 mmol/litre for non-HDL cholesterol, taking into account the trade-off between increasing medication (the committee noted that a combination pill of Atorvastatin and ezetimibe is available in the USA),

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				cause confusion among those who believe their cholesterol to be adequately under control with a statin alone, and adherence may be lower for people on 2 pills rather than 1".	minimising risk and the burden of implementation which is most likely to fall within primary care. We have edited recommendation 1.7.11 to make it clear that ezetimibe should be considered to reduce CVD risk further. This would depend on several factors and would be discussed as part of shared decision making with the person.
PrescQIPP CIC	Guideline	007	014 - 018	1.6.13 We agree with the 4th line placement of bempedoic acid in the main pathway and as an alternative option in patients who are intolerant to a statin It should be made clear that bempedoic acid should only be prescribed in combination with ezetimibe, not on its own. The recommendation needs to be re-worded to make it clear that a PCSK9 inhibitor OR inclisiran can be added to ezetimibe plus bempedoic acid, but that a PCSK9 inhibitor and inclisiran should not be prescribed concurrently.	Thank you for your comment. Recommendation 1.10.2 has been edited and now refers to the technology appraisals (in alphabetic order) for information of treatment combinations.
PrescQIPP CIC	Guideline	007	021	1.6.14 We are unclear as to why the new instruction for primary care is that non-HDL or LDL cholesterol should be 'calculated'. This may confuse primary care clinicians as currently most labs now provide non-HDL levels – clinicians don't currently have to do any 'calculating'. This is a simple calculation for non-HDL but less so for LDL. If this is to be the case then the equation to be used for LDL calculation (and what to do if triglyceride > 4.5 mmol/l) should be added, and will need to be embedded in GP clinical systems.	Thank you for your comment. Recommendation 1.11.1 now refers to a full lipid profile which could be non-fasted or fasted. This is defined in the 'terms used' section and the word calculate has been removed but it is expected that this calculation will be performed by the laboratory.

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				We are also not clear why both non-HDL and LDL cholesterol would be needed, given that the target in 1.6.1 states that LDL would only be used if non-HDL is not recorded. It should be made clear that the blood test for non-HDL-C does not need to be fasting.	
PrescQIPP CIC	Guideline	007	024	1.6.15 We support the recommendation for annual medication reviews and amendment to include all lipid lowering therapies	Thank you for your comment.
PrescQIPP CIC	Guideline	007	028 , 029	1.6.15 The recommendation "Consider an annual non-fasting blood test for non-HDL cholesterol to inform the discussion" does advise measuring non-HDL (rather than calculating) and is inconsistent with recommendation in 1.6.14.	Thank you for your comment. Recommendations 1.11.1 and 1.11.9 have been edited and now recommend a full lipid profile which could be non-fasted or fasted.
PrescQIPP CIC	Guideline	007 and 008	026 - 029 001 - 004	1.6.9 and 1.6.10 Our experience is that many clinicians are not aware of the significance of the wording "offer" and "consider" within NICE guidelines. We believe that it would therefore be appropriate for the guideline to be more explicit in this section, explaining that the "offer" recommendation for ezetimibe denotes that there is stronger evidence/cost-effectiveness for using ezetimibe ahead of a PCSK9 inhibitor or inclisiran, which have a "consider" recommendation.	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
PrescQIPP CIC	Guideline	009	General	The economic model is a forecast assumption model, and does not provide any clarity regarding the total number of patients requiring injectable therapy. ICBs will need an	Thank you for your comment. Table 34 indicates the proportion of people with CVD and on a statin that

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				understanding of the patient numbers involved to ensure appropriate capacity is made available in primary and secondary care for adoption of the updated clinical guideline.	would need to be escalated at a target of 2.0 mmol/litre LDL-C. A resource impact report and tool will accompany this guideline update at the time of publication. This will include estimates of the number of patients that would require escalation to injectable therapies and the associated capacity impact.
PrescQIPP CIC	Guideline	General	General	It would be useful to have a visual algorithm to support the implementation of this guideline – ideally produced instead of, or to align with the current national guidance produced by the Accelerated Access Collaborative.	Thank you for your comment. The recommendations have been edited to make it clear that all of the relevant treatment options should be considered, in people above the target, in accordance with the NICE technology appraisals. A visual algorithm of the treatment pathway was therefore not thought to be helpful in explaining the recommendations of this guideline.
PrescQIPP CIC	Guideline	General	General	The commercial access price for inclisiran is only guaranteed until July 2024 (i.e. another 6 months). ICBs will need urgent assurance regarding ongoing pricing plans for inclisiran and re-negotiation of the contract price. The NICE TA for inclisiran is also due to be reviewed by July 2024 to ensure ongoing clinical and cost effectiveness. If a pricing agreement is not secured and the TA becomes a negative position, CG181 will need to be updated accordingly to reflect this.	Thank you for your comment. The NICE TA may be updated if the pricing changes and the impact of this on the recommendations in this guideline will be considered then.
Primary Care Cardiovascular Society	Guideline	005	005	1.6.1 We believe the wording of this should be amended, because all major trials in lipid modification, and lipid	Thank you for your comment. Recommendation 1.7.1 has been.. The trial evidence for LDL was the more robust both in terms of cholesterol reduction for each

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				lowering licensing use LDL-C as the benchmark. In your document you state that 'The evidence linking non-HDL cholesterol to major cardiovascular events was **much weaker** than for LDL cholesterol and therefore the LDL model was favoured as the most evidence-based approach' . We agree overwhelmingly with this statement and believe this should override cost effectiveness decisions based on potentially flawed lipid lowering escalation sequencing contained in this document. We appreciate that many laboratories in the UK do not provide a full lipid profile and often just report TC, HDL-C and HDL-C:TC ratio. As a society we believe there should be a National drive for all laboratories to report LDL-C using the Sampson's formula even on non-fasting samples. We accept NICE does not have the remit to suggest this. Furthermore, many clinicians and certainly patients do not understand non-HDL-C, laboratories do not always report it and patients and clinicians may use TC as a target, which we know is not ideal. Many also believe that LDL based on non-fasting samples, differ little from a fasting sample (except in the context of high triglyceride levels >4.5mmol/L). We also believe suggesting LDL-C levels of 2.0 mmol/L or less is confusing and at odds with every International guideline, QOF CHOL002 indicator target, National CVDPrevent targets, AHSN and AAC guidelines which all suggest an LDL-C of 1.8mmol/L or less. In primary care	treatment and the relationship between cholesterol reduction and CVD outcomes. This evidence determined the most cost-effective target in the economic model (see the committee's discussion of the evidence in evidence review D). However, non-HDL is also given in the recommendation. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. Cost effectiveness has not been considered by other guidelines. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Recommendation 1.7.11 recommends that Ezetimibe can be considered to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is achieved. The model used the distributions from the CPRD dataset, where a 2.0 LDL cholesterol equivalent target

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				we have been working to this lower target and changing it will confuse clinicians and patients. Furthermore you state that 'The committee agreed lipid levels should be reduced as much as possible in people with CVD', but then go on to recommend targets that are far too high for this high risk group and at odds with 110xcel110size evidence-based guidelines, National targets and good clinical practice. Your statement that 'people respond differently to statins and other lipid-lowering treatments and it is not cost effective to offer the full range of treatments to everyone with CVD' is actually precisely why everyone with CVD, all of whom are at highest risk of further events and premature mortality, should have the opportunity to receive the full range of treatments, that provides the opportunity to reduce their LDL-C and hence optimally in line with the TA. Our reasoning here is 1. Currently we have no way of identifying non responders to specific therapies in the NHS (genotyping for individual statin non response are available but not to NHS patients) 2. Your statement is dependent on a best guess of best sequencing, which we believe is flawed (see **1.6.9** comments) Trial evidence 110xcel110sized in several meta-analyses and from individual trials suggest that the lower the LDL-C the better in terms of reducing CV events and mortality. We know that LDL-C levels are the main driver of development of atherosclerotic CVD and plaque	that would lead to the same proportion (42%) of people escalating would be 2.6 non-HDL cholesterol. An alternative approach would be to use the Friedewald equation and insert the mean triglyceride level along with the LDL cholesterol of 2.0 mmol per litre. For this we have used 1.4 mmol per Litre, which is the mean triglyceride level in our dataset at an LDL of 2.0 (rather than assume 1.7 mmol/litre). This approach also indicates a non-HDL cholesterol target of 2.6 mmol per litre. You get 2.8 mmol per Litre if you assume a triglyceride level of 1.7 but this does not seem to be consistent with our data. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.

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				development, and higher levels for prolonged periods drive larger plaques that develop earlier. ESC guidelines recommend LDL-C of 1.4 or lower for all ASCVD patients considered to be high risk, and 1.0 or less for very high risk disease (recurrent events or progression of disease within 2 years). Surely NICE should be following these evidence based guidelines for the benefit of patients in reducing CV events, CV mortality, hospitalisations and hence long term benefits to NHS budgets. Furthermore, LDL-C 2.0mmol/L actually equates to non-HDL-c of 2.8mmol/L or less. We would recommend the following wording: **"For secondary prevention of CVD aim for LDL-C levels** of **1.8mmol/L or where LDL-C is not recorded non-HDL-C levels of 2.6 mmol/L or less"**	
Primary Care Cardiovascular Society	Guideline	006	001	1.6.4 We would recommend that lipid samples should be checked at 6-8 weeks after statin or LLT treatment. The benefits are seen from 4 weeks onwards and more rapid titration will reduce risk quicker but more importantly keep lipid management in the 'mind' of clinicians and patients and enable compliance/persistence in taking medication.	Thank you for your comment. Recommendation 1.7.5 has been edited and now refers to 2 to 3 months after starting treatment.

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Primary Care Cardiovascular Society	Guideline	006	027	1.6.9 We believe this is too simplistic and sequencing should depend on LDL-C levels, as per licensing for inclisiran (LDL-C 2.6 or greater), PCSK9i (LDL-C 3.5 or 4.0 or greater depending on level of risk. If LDL-C 2.6 or greater on high dose statin then adding ezetimibe to all patients is very unlikely to achieve an LDL 1.8 or even 2.0. If LDL drops below 2.6 but not at target then you are closed out of licensing indication to initiate Inclisiran. The NICE committee should recommend sequencing in line with AHSN/AAC guidance depending on LDL-C (or non HDL-C where no LDL recorded) levels.	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
Primary Care Cardiovascular Society	Guideline	007	001	1.6.10 We suggest sequencing is clear as per AHSN/AAC guidance, and include Bempedoic Acid or Bempedoic acid plus ezetimibe, given we now have positive CV outcome data from the CLEAR OUTCOMES trial in Primary and Secondary Prevention.	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to avoid any potential conflict with the relevant NICE technology appraisals and to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs. Bempedoic acid has been referred to in recommendation 1.10.2 for people in whom statins are contraindicated or who are statin intolerant based on TA694.

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Primary Care Cardiovascular Society	Guideline	007	020	1.6.14 Consider changing to 6-8 weeks for reasons given in 1.6.4.	Thank you for your comment. Recommendation 1.10.1 now recommends at 2 to 3 months but this does not preclude a test being carried out earlier.
Primary Care Cardiovascular Society	Guideline	007	024	1.6.15 Consider an annual non-fasting blood test for LDL-C and/or non-HDL-C to inform the discussion. **IND2022-133** We would strongly recommend for reasons outlined in section 1.6.1 that the wording should read: "The percentage of patients with CVD in whom the last recorded LDL-C (measured in the preceding 12 months) is 1.8 mmol/L or less, or last recorded non-HDL-C (measured in the preceding 12 months) is 2.6mmol/L or less, if LDL-C is not recorded	Thank you for your comment. We have added full lipid profile to recommendation 1.11.9. The indicator has been amended to align with NG238 (formerly CG181). The construction now searches for LDL first, and if not found, non-HDL.
Quality Standards and Indicators Team	EIA	001		3.2 Data from CVDPREVENT reports that females are less likely to reach cholesterol treatment targets compared to males. **The latest data from CVDPREVENT reports that 27.8% of all people with recorded CVD had non-HDL cholesterol less than 2.5mmol/l or LDL-cholesterol less than 1.8mmol/l.** • 30.88% of males achieved target • 23.07% of females achieved target	Thank you for your comment. This information has been added to the Equalities Impact Assessment form but no changes were made to the recommendations as this is an implementation issue.

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				Source: Data Explorer | CVDPREVENT	
Royal College of General Practitioners	Guideline	005	005	Rec 1.6.1 The committee has decided to adopt a fixed target lipid level for secondary prevention. The following are potential implications that should be taken into consideration. We are concerned that this: • Creates a conflict between primary and secondary prevention strategies. In primary care, individuals are repeatedly told that there is no universal "target" for cholesterol. Setting a fixed target will discourage individuals with relatively good lipid profiles from taking statins. Setting a fixed target for secondary prevention will generate confusion among patients and clinicians. Since there has been significant controversy within primary care regarding lipid management for many years, the fixed target and confusion that will surround it are likely to cause more distrust amongst primary care clinicians. Therefore, they are less likely to use the guidance across primary care.	Thank you for your comment. The committee did consider retaining the 40% reduction from baseline (and even 50% as per the ESC guidance) for secondary prevention patients and then the target would be to achieve either an absolute level or the % reduction, which ever produced the lowest LDL-c (or non-HDL-c result). However, whilst this appeared to be scientifically more robust, the pragmatics were such that the committee considered it would produce confusion and (in many cases) be impossible to implement and therefore the more simplistic approach was to adopt an absolute value as the threshold for escalation.
Royal College of General Practitioners	Guideline	005	010	Rec 1.6.2 This recommendation is not clear. If clinicians are to offer everyone with CVD 80mg of atorvastatin, what is the rationale behind measuring the cholesterol and lipid profile? If the measurement is taken and an individual's non-HDL is already <2.6, (the cut off described in the document), then prescribing atorvastatin (80 mg) will not resonate well with patients or clinicians. Clarification between these 2 recommendations (1.6.1 and 1.6.2)	Thank you for your comment. The evidence shows that the lower the bad cholesterol the better the outcomes and statins have additional benefits beyond just the magnitude of cholesterol lowering and are cost effective at any levels of baseline cholesterol, thus everyone when diagnosed with atherosclerotic CVD should be offered a statin irrespective of lipid levels. Knowing the baseline is important since it enables a

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				should therefore be made clear to ensure the clinician and patient know which approach is better. Reduce to 2.6 (rec 1.6.1) or treat despite their cholesterol level (rec 1.6.2). The RCGP prefers the approach to treatment (rec1.6.2) rather than the target level (rec 1.6.1).	clinician to assess response/ adherence (and the likelihood of hitting the target with statin alone) and will pick up other problems such very low HDL levels/very high triglycerides which may require other interventions (lifestyle) or specialty input.
Royal College of General Practitioners	Guideline	007	001	Rec 1.6.10 This recommendation is not clear. Does the committee mean "If the lipid target….is not achieved using high intensity statins and ezetimibe then consider escalating treatment with the addition of alirocumab, evolocumab OR inclisiran"? Clarification is needed. If the target is not achieved after adding ezetimibe, should alirocumab be considered? Additionally, should alirocumab be considered if a patient cannot tolerate ezetimibe, or if it is contraindicated or declined?	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to avoid any potential conflict with the relevant NICE technology appraisals and to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
Royal College of General Practitioners	Guideline	007	005	Rec 1.6.11 This recommendation is not clear. It appears to suggest adding ezetimibe even if the person has achieved the target lipid profile. If a person is to be given high intensity statins irrespective of their lipid profile (rec 1.6.1) and if ezetimibe is to be given, irrespective of whether they have reached the target level (rec 1.6.11) could the committee consider simplifying the guidance and state "offer high intensity statin and ezetimibe to everyone with CVD" ?	Thank you for your comment. The evidence showed (see evidence review D) that ezetimibe was cost effective regardless of the person's lipid levels, the committee therefore decided that it could be considered for people with lipid levels below the agreed targets of 2.0 mmol/litre for LDL cholesterol and 2.6 mmol/litre for non-HDL cholesterol, taking into account the trade-off between increasing medication (the committee noted that a combination pill of Atorvastatin and ezetimibe is available in the USA), minimising risk and the burden of implementation

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				Indeed, if this is the aim of this recommendation, there will need to be: • Clarification on why measuring lipids is of use given that we are treating, irrespective of the target level with both statins and ezetimibe. • Further clarifications regarding the evidence of ezetimibe in order to build trust within the primary care community to use this drug. For many years primary care clinicians were told not to prescribe ezetimibe. Therefore, clinicians and patients will require a clear rationale for the benefits of adding ezetimibe, especially if a patient has already achieved the target. Clarification on whether all people with CVD should be offered both a high intensity statin **and** ezetimibe at all times, as otherwise there is a risk of medicolegal challenges if a patient, who is at target with a high dose of statin, experiences another CV event and was not "considered" for ezetimibe.	which is most likely to fall within primary care. We have edited recommendation 1.7.11 to make it clear that ezetimibe could be considered to reduce CVD risk further. This would depend on several factors and would be discussed as part of shared decision making with the person. The recommendation is aimed at people who have been started and then monitored for their response to initial statin treatment.
Royal College of General Practitioners	Guideline	007	014	Rec 1.6.13 Clarification is required. The wording should explicitly state whether these are in in addition to ezetimibe or alternatives to it. E.g., "If the lipid target for secondary prevention is not achieved on ezetimibe alone (or ezetimibe is not tolerated), consider alirocumab, bempedoic acid, 16 evolocumab OR inclisiran".	Thank you for your comment. Recommendation 1.10.2 has been edited and now refers to the technology appraisals in alphabetic order. The TAs provide recommendations on whether the treatments are in addition to ezetimibe or are alternatives.
Royal College of	Guideline	007	020	Rec 1.6.14 It is disappointing that after years of not requiring annual lipid profiles that we are returning to annual blood tests for those on statins. This will require	Thank you for your comment. Recommendation 1.11.9 recommends that a full lipid profile is offered. In the experience of the committee this reflects current

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General Practitioners				additional resources in primary care including additional phlebotomy time and GP time to review blood test results along with the administrative burden on receptionists contacting patients with results. We are concerned that this additional work has not been adequately covered in the cost analysis.	clinical practice and is reflected in the current QoF indicator.
Royal College of General Practitioners	Guideline	010	018	It is our belief, following consultations with experts, that the estimation aligning a non-HDL of 2.6 with an LDL of 2.0 is incorrect. The RCPG believes that an LDL of 2.0 will align with a higher value of non-HDL which builds further mistrust among the primary care community and poses a risk to the guidance not achieving large scale implementation. The rationale does not reassure us on this point and will require strengthening if the committee does not raise the non-HDL target level.	Thank you for your comment. The committee discussed using equations such as the Friedewald and Sampson but due to their potential limitations, for example the former has not been formally validated in a statin treated population, preferred to use the distributions from the CPRD dataset, where a 2.0 LDL cholesterol equivalent target that would lead to the same proportion (42%) of people escalating would be 2.6 non-HDL cholesterol. An alternative approach would be to use the Friedewald equation and insert the mean triglyceride level along with the LDL cholesterol of 2.0 mmol per litre. For this we have used 1.4 mmol per Litre, which is the mean triglyceride level in our dataset at an LDL of 2.0 (rather than assume 1.7 mmol/litre). This approach also indicates a non-HDL cholesterol target of 2.6 mmol per litre. You get 2.8 mmol per litre if you assume a triglyceride level of 1.7 but this does not seem to be consistent with our data. Information has been added to the rationale on how the non-HDL was calculated for the recommendation.

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Royal College of General Practitioners	Guideline	General		The RCGP believes that this guideline requires further clarity regarding the steps to treat and escalate treatment and therefore would request the committee to consider the recommendations from the perspective of a clinician, seeing them for the first time. We have made comments on the specific recommendations that we believe require clarification and simplifying. It is important to consider that there has been significant controversy surrounding lipid management in primary care for many years, worsened by the recent Inclisiran controversy. For this guideline to be taken up by primary care, it needs to be clear and simple. Currently, the complication and lack of clarity is likely to lead to reluctance to use the guidance in primary care.	Thank you for comment. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
Royal College of General Practitioners	Guideline	General		We are disappointed that there is no mention of bempedoic acid in the consultation which is a drug that can be used for lipid modification. We request NICE to review the guidance and explain where bempedoic acid fits in the guidance. It is essential for GPs that all medication is considered, using one simple guidance to build trust with both patients and clinicians. The response stating that this was out of scope of the guidance will not be accepted by GPs. This poses a risk of building mistrust in the guidance, with no clear rationale of why it was omitted.	Thank you for your comment. Recommendation 1.10.2 includes bempedoic acid. The recommendation is based on TA694 which is for people in whom statins are contraindicated or not tolerated.
Royal College of	Guideline	General		The RCGP believes that the cost effectiveness of treatment escalation has been miscalculated by NICE.	Thank you for your comment. The model does include the cost of additional tests and contacts in the base

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General Practitioners				NICE do not take in to account the true costs within primary care for medication escalation which includes reception, non-clinical administrative time, additional blood tests, clinical review of results and additional patient contact time. This requires correction before progressing with this guidance.	case. More costs were included in a sensitivity analysis but these did not change the most cost effective target.
Royal College of General Practitioners	Indicator			The RCGP does not support the use of the indicator with a target level of non-HDL or LDL and strongly recommends that this approach be changed, aiming to improve the number of people on treatment, rather than using target levels that will simply add to the significant mistrust in primary care regarding lipid pathways. This is where the evidence lies. We would recommend that the committee considers an alternative indicator, such as "The percentage of patients with CVD who are prescribed high intensity statins and ezetimibe". The guidance states that people with CVD should be offered high intensity statins, irrespective of their lipid levels, plus ezetimibe, irrespective of their target levels, a position that we support as the evidence base is strong for this approach. These are significant changes to treatment pathways, which will require buy in from primary care and will therefore take time to implement. By simplifying the indicator to focus on improving treatment regimes, i.e high intensity statins and ezetimibe, it will build trust in patients and the profession, which is at an all-time low regarding	Thank you for your comment. The current NICE menu indicator NM212 (general practice level indicator suitable for us in the QOF) measures the percentage of patients with cardiovascular disease who are currently treated with a lipid lowering therapy. This includes statin and non-statin therapies. Previous indicator work in this area suggests that intensity of statin therapy is not extractable using GPES. We will continue to explore potential new indicators relevant to other aspects of the lipid management pathway.

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				lipid pathways. Improving prescribing, and then potentially allowing for target-based approaches in the future. We understand the political pressure to use a target, and recognise the difficult position that NICE is in. However, RCGP believes that to significantly improve patient care and avoid the controversy of recent years relating to lipid prescribing, ensuring primary care uses the new guidance, a treatment based approach to the indicator is the best solution. A treatment approach indicator will unify primary care, build trust and improve prescribing, which in turn, will improve patient care and prevent more CVD events. Using a target approach will simply remind primary care of the push to use inclisiran in primary care which will immediately create barriers, risking the implementation of the guideline. If you intend to incentivise primary care using QuOf to prevent CVD, we strongly suggest that you use the medication based approach rather than the target level approach. It is more likely to be accepted and therefore achieved by primary care, with less exception reporting. Once primary care is then prescribing the medication, the indicator could move on to consider target level to further enhance treatment in future years.	

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Royal College of Nursing	Guideline	005	005	1.6.1 In summary of the evidence, the lower the LCL-C the lower the event rate. Hence, why does the guidance suggest a non-aligned target that also seems disadvantages patients? From a guideline, clinical, or health economics point of view this does not compute.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 (used in the QoF) compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would not be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. Recommendation 1.7.11 recommends that ezetimibe can be considered to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is achieved.
Royal College of Nursing	Guideline	005	005	1.6.1 It would be good to have further clarification regarding the recommendation in 1.6.1, i.e. why an LDL-C target of 2mol/l is stated? This neither aligns with QOF 2023, European Atherosclerotic Society/ European Society of Cardiology Dyslipidaemia Guidance 2019 nor with the European Society of Cardiology Guidance CVD and Diabetes 2023.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. Cost effectiveness has not been considered by other guidelines. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to

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				These guidance recommendations all use a secondary prevention target of 1.8 mmol/lt.	other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator.
Royal College of Nursing	Guideline	General	General	The Royal College of Nursing invited members who work in this area of health to review the NICE draft guidance on our behalf. The comments below reflect the views of our reviewers.	Thank you for your comment.
Royal College of Physicians (RCP)	Guideline	General	General	The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our representative and would like to comment as follows.	Thank you for your comment.
Royal College of Physicians (RCP)	Guideline	General	General	Unfortunately, there are major flaws and inaccuracies in the guideline. There is a lack of understanding of clinical care pathways, discordance with the QoF and the NHS Accelerated Access lipid pathway in the UK, in addition to being out of step with major international guidelines.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator.

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					Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. NICE's implementation support team plan to work with partners to align initiatives and pathways if requested.
Royal College of Physicians (RCP)	Guideline	General	General	An LDL-C of 2.0mmol/L does not equate to a non-HDL-C of 2.6mmol/L. The relationship is well established and ESC/ EAS, AHA/ACC guidelines when they use non-HDL-C as secondary target these are the equivalent LDL-C and non-HDL-C levels used. Why or how the committee could come up with a different parameter compared to the rest of the world is unclear and surprising. An LDL-C 2.0mmol/L, then the equivalent non-HDL-C is 2.8mmol/L.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. Using the distribution of LDL cholesterol levels for the population with CVD and on a statin in the clinical practice research datalink (CPRD) dataset, 42% of people had LDL cholesterol levels of 2.0 mmol per litre or more. Using the same data, the threshold for non-HDL cholesterol that would produce an identical number of people being escalated for treatment was 2.6 mmol/litre. An alternative approach would be to use the Friedewald equation and insert the mean triglyceride level of 1.4 mmol per Litre along with the LDL cholesterol of 2.0 mmol per litre. This approach also indicates a non-HDL cholesterol target of 2.6 mmol per litre. We think that you have estimated a non-HDL target of 2.8 using the Friedewald equation, using a triglycerides level of 1.7 mmol/litre. We are not sure the basis for

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					that assumption, which does not seem to reflect the population in our dataset."
Royal College of Physicians (RCP)	Guideline	General	General	The QoF indicator for those with ASCVD is 1.8mmol/L equivalent to a non-HDL-C of 2.5mmol/L	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator
Royal College of Physicians (RCP)	Guideline	General	General	The NHS Accelerated Access Lipid implementation pathways cite a decision threshold of non-HDL-C of 2.5mmol/L or an LDL-C of 1.8mmol/L as the decision pivot point for consideration of escalation of therapy. For instance, if the LDL-C was > 2.6 go to inclisiran, or a monoclonal if LDL-C > 3.5 or 4mmol/L depending upon CV risk. Below an LDL-C of 2.6 the advice was to add in ezetimibe if statins had been optimised. These were the NICE TA approved cost-effective thresholds therefore it is surprising that this	Thank you for your comment. We have revised Figure 1 so that it more accurately reflects the national pathway. We acknowledge that not everyone above the target will be escalated to ezetimibe. We have maintained this in the model base case, as this was the most cost-effective pathway. However, we have added sensitivity analyses to the model, where alternative treatment pathways were followed. In two of these analyses, the optimal target remained the same. In a third, the optimal target was slightly higher. The

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				is not how the data were modelled but rather sequentially. This is not how clinicians practice, therefore the model used does not reflect clinical practice nor is it concordant with HTAs.	committee decided to stick with the target of 2.0 mmol per litre for LDL cholesterol. The recommendation to offer ezetimibe plus a statin has been removed to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
Royal College of Physicians (RCP)	Guideline	General	General	A different LDL-C to those in points 2 and 3 will cause confusion and difficult to implement.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator.

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					The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
Royal College of Physicians (RCP)	Guideline	General	General	From an efficacy and evidence point ESC guidelines since 2019 recommend an LDL-C of 1.4mmol/L (2019) whilst AHA/ACC (2020) recommend 1.8mmol/L with the option in those with additional comorbidities to aim for 1.4mmol/L (ACC 2023).	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. Recommendation 1.7.11 recommends that ezetimibe can be considered to reduce CVD risk further e.g., due

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					to comorbidities, even if the lipid target for secondary prevention of CVD is achieved.
Royal College of Physicians (RCP)	Guideline	General	General	The current model for cost effectiveness uses inclisiran at all levels of LDL-C and after ezetimibe. This is not how the NICE TA was conducted. For instance, you would for a patient on statins with an LDL-C of 2.8, not go to ezetimibe as this would bring their LDL-C down to 2.1mmol/L leaving them potentially at high CV risk. You would here opt for inclisiran as per the HTA which would bring the LDL-C to 1.4mmol/L. In the first case you have only changed risk by about 18% from statins in the latter by 30%.	Thank you for your comment. We acknowledge that not everyone above the target will be escalated to ezetimibe. We have maintained this in the model base case, as this was the most cost-effective pathway. However, we have added sensitivity analyses to the model, where alternative treatment pathways were followed. In two of these analyses, the optimal target remained the same. In a third, the optimal target was slightly higher. The committee decided to stick with the target of 2.0 mmol per litre for LDL cholesterol. The recommendation to offer ezetimibe plus a statin has been removed to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
Royal College of Physicians (RCP)	Guideline	General	General	The model used is discordant with other data published (McKay et al 2022 EJPC) using CPRD and linked ONS/HES data where the ASCVD cohort where the 10-year observed risk of CV death, non-fatal Mi or stroke was 29% for men and 26% for women and baseline non-HDL-C was ~3.4mmol/L.	Thank you for your comment. We do not agree that the CPRD analysis results are discordant with those of McKay et al 2022. The numbers you cite are not that dissimilar to those in the model. Furthermore, our cohort were patients on a statin and therefore we

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				The models cited using CPRD assume that CV risk depends upon age, gender and cholesterol which is an oversimplification. Moreover, the LDL-C and non-HDL levels in CPRD and event rates are much lower than reported elsewhere which calls into consideration the whole economic model and baseline risk is lower than in the other studies similar the LDL-C and non-HDL-C are lower which affects estimates of baseline risk and hence cost effectiveness.	would expect them to have lower cholesterol levels than a broader population. In addition to age, gender and cholesterol, we also differentiated those who had a CV event in the last 12 months. The method of risk estimation was wholly sufficient to estimate the risk levels at the population-level in our target population of people with CVD on a statin. You suggest that both cholesterol and CV risk have been under-estimated. If the population risk level has been under-estimated, it would mean that the model is under-estimating the proportion requiring escalation and the subsequent cost impact. However, even if this is the case, which we dispute, the most cost-effective target in the model would still be accurate, as long as the CV risk levels correlate with the LDL-C levels, which you seem to imply.
Royal College of Physicians (RCP)	Guideline	General	General	Finally, there is a fundamental flaw in using all-cause mortality rather than CV mortality in the model. Lipid lowering reduces deaths from CV causes but has no impact on non-CV deaths. If CV deaths account for instance 20% of all deaths (Global Cardiovascular risk consortium NEJM 2023), you dilute the potential benefit of any treatment. This in part explains the very different interpretation for cost effectiveness of	Thank you for your comment. The use of all-cause mortality is not a flaw since, as well as using all-cause mortality from a CVD population we have also taken the Cholesterol Treatment Trialists' Collaboration (CTTC) treatment effect on all-cause mortality from a CVD population (and not a mixed population). The CTTC effect on all-cause mortality is estimated in the same way as the other CTTC effects and is equally

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				inclisiran at an LDL-C > 3.1 vs the NICE TA which stated 2.6mmol/L. This is partly acknowledged in the section talking about this. "The economic model finds inclisiran to be cost effective at LDL-C > 3.1 instead of 2.6 + and recommends: The treatment-specific targets analysis found that it was most cost-effective to give ezetimibe to everyone and prescribe inclisiran solely to those with an LDL cholesterol exceeding 3.1 mmol/litre. This is contradicting the TA733." The rather weak justification cited is " The TA model applied a treatment effect to CVD mortality rather than all-cause mortality. The life-years gained in the TA model were greater because the baseline risk of modifiable CVD mortality was much higher."	valid since it is in a CVD population. Hence there should be no dilution of effect. Although in the model the optimal treatment threshold for inclisiran was 3.1 mmol/litre of LDL-C, we have since noted that the net health benefit for an inclisiran treatment threshold of 2.6 mmol/litre in the guideline model is actually only slightly lower than that of 3.1 mmol/litre. Therefore, inconsistencies with the TA are not as great as they at first seem. If we had used the baseline risk of CV mortality from the TA then we would have reached a lower optimal target. However, there were good reasons for not doing so. In the TA model, CVD mortality was estimated over only one-year, for people who had mostly had a CV event in the last year or two. It was then assumed that the CVD mortality would increase by 5% a year, every year thereafter. Our approach is better because it stratified event rates by age, sex and differentiated between mortality in the prevalent and acute populations. Furthermore, by applying an all-cause mortality treatment effect we avoided problems associated with defining modifiable CVD mortality.
Ruddington Medical Centre	Guideline	007	005	1.6.11-While assessing Lipid targets for secondary prevention of cardiovascular disease, it should include both Low-Density Lipoprotein c and fasting Triglyceride	Thank you for your comment. The committee agreed that there is insufficient data to comment or establish a TG target for CVD risk lowering.

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				levels which together form the residual risk estimation. Ezetimibe has not shown any significant impact on Triglyceride levels in this clinical scenario. Icosapent Ethyl has shown evidence in reduction in residual risk reduction for cardiovascular disease as per the REDUCE-IT trial	The committee advise measurement of a full lipid profile where available to allow clinicians to consider this in their decision making (recommendations 1.11.1 and 1.11.9) but this can be fasted or non-fasted. These recommendations form part of the guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification. That guideline includes recommendations on omega 3 fatty acid compounds, and on combination therapy (1.12.5 – 1.12.7) which include reference to icosapent ethyl in line with NICE TA805.
Ruddington Medical Centre	Guideline	General	General	In my clinical practice, patients treated with high-intensity statin for secondary prevention of cardiovascular disease remain at high risk of having further coronary events which would have a further impact on their quality of life. It is imperative that all factors which contribute to residual risk are looked at while managing such patients. Just concentrating on Low-density lipoprotein fails to address the issue. Icosapent Ethyl has a pleiotropic (non-lipid) mechanism of action which has been found to be cost-effective as per NICE TA 805 and should also be included in recommendations when considering secondary prevention in these high-risk patients.	Thank you for your comments. The committee agree that a number of factors need to be considered when trying to reduce CVD risk. Recommendations 1.7.4 and 1.11.11 refer to factors such as diet and lifestyle. The recommendations consulted on form part of the guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification. Recommendations 1.12.5 - 1.12.7 (on omega 3 fatty acid compounds, and on combination therapy) in that guideline include reference to icosapent ethyl in line with TA805.
Rycroft Health Associates Ltd	Guideline	005	005	1.6.1 We are concerned that this recommendation may imply that patients achieving an LDL-C between >1.8mmol/L and <2mmol/L on optimised statin and ezetimibe may be at an increased risk of cardiovascular events compared	Thank you for your comment. Recommendation 1.7.11 recommends that ezetimibe can be considered to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is achieved.

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				with existing recommendation of reducing LDL-C to below 1.8mmol/L. Once the patient's LDL-C is <2.0mmol/L the guideline would imply no further lipid modifying therapy will be required despite growing evidence e.g., the ESCs guideline to target 1.4mmol/L, that tighter control of LDL-C helps reduce cardiovascular events.	
Rycroft Health Associates Ltd	Guideline	006	027	1.6.9 We are concerned that this recommendation may delay optimisation of lipid levels and increase primary care workload, particularly in patient cohorts with an LDL-C level of >2.5mmol/L on optimised statins, given the % reduction in LDL-C expected from adding ezetimibe therapy.	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
Sanofi	Guideline	005	005 – 007	There are a group of patients with baseline LDL-C's in range of ~5.5 mmol/L to 6.5mmol/L who are unlikely to get to an LDL-C target of < 2.0 mmol/L on high intensity statin + ezetimibe (based on average reduction estimations of ~50% and 20%, respectively) but are not eligible for any PCSK9-based therapy (based on the reimbursement thresholds in the NICE technology appraisals (TA's)) – these patients end up in treatment limbo. It is not clear from the guideline how to manage these patients?	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed so make it clearer that a treatment pathway is not being recommended. The population in the TA recommendation is specified as people in whom low-density lipoprotein cholesterol (LDL-C) concentrations are persistently 2.6 mmol/l or more, despite maximum tolerated lipid-lowering therapy, that is: • maximum tolerated statins with or without other lipid-lowering therapies or

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					• other lipid-lowering therapies when statins are not tolerated or are contraindicated. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the TAs. On an individual basis, people could be offered lipid lowering treatments to meet their cholesterol target even if they are below the LDL thresholds in the TA.
Sanofi	Guideline	005	005 – 007	The LDL-C target of < 2.0 mmol/L appears to go against generally accepted convention that the non-HDL target is listed as 0.8mmol/L higher than the LDL-C target as seen in other national guidelines (ESC, AHA, EASD) – again creating confusion among clinicians.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness (unlike other guidance) to ensure the optimal allocation of resources for the NHS. They decided that there should be a non-HDL target in addition to the LDL target. The committee discussed using equations such as the Friedewald and Sampson but due to their potential limitations, for example the former has not been validated in a statin treated population, preferred to use the distributions from the CPRD dataset, where a 2.0 LDL cholesterol equivalent target that would lead to the same proportion (42%) of people escalating would be 2.6 non-HDL cholesterol.

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					An alternative approach would be to use the Friedewald equation and insert the mean triglyceride level of 1.4 mmol per Litre along with the LDL cholesterol of 2.0 mmol per litre. This approach also indicates a non-HDL cholesterol target of 2.6 mmol per litre. We think that the convention of setting a non-HDL target of 0.8 mmol/litre above the LDL target is based on assumption that triglycerides are 1.7 mmol/litre but this does not seems to be consistent with our data.
Sanofi	Guideline	005	005 – 007	The LDL-C target of < 2.0 mmol/L contained herein is different from both the new Quality Outcomes Framework (QOF) indicator CHOL002 and the National Lipid Management pathway (both list targets of non-HDL-C < 2.5mmol/L or LDL-C < 1.8mmol/L) – different numbers lead to confusion among clinicians, particularly for non-lipid experts in primary care. Targets that have been agreed through clinical consensus and clinical output, like the National Lipid Management pathway, should be used throughout for clarity.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024.

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Sanofi	Guideline	005	005 – 007	While Sanofi welcome a target-based approach we do not agree with the target of < 2.0 mmol/L for LDL-C. Current ESC/EAS 2019 Guidelines advocate a target of LDL-C < 1.4 mmol/L in very high risk patients based on the current clinical and genetic evidence that support the concept that reduction in LDL-C levels below their current recommended target provides additional clinical benefit to patients without adversely impacting patient safety (JUPITER, IMPROVE-IT, ODYSSEY OUTCOMES, FOURIER, CLEAR OUTCOMES). While we obviously accept that economic factors are considered, this LDL-C target is based solely on economics and does not consider the more recent clinical evidence suggesting that lower LDL-C is better in terms of clinical outcomes.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The economic modelling incorporated data from clinical trials, including IMPROVE-IT, ODYSSEY OUTCOMES, FOURIER, and CLEAR OUTCOMES. The cost per QALY of a target of 1.8 (used in the QoF) compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. Treatment related adverse events were considered by the committee when making their recommendations (see evidence report A).
Sanofi	Guideline	006 – 007	026 – 004	It is stated that clinical evidence is important to inform recommendations, yet in the draft guideline no guidance is given on the other therapies on the basis of availability of positive cardiovascular outcomes trial or long-term safety data. Note that several other therapies that lower LDL-C have not achieved positive cardiovascular outcomes data (CETP inhibitors, Niacin); therefore, to assume that all agents that lower LDL-C will impact CV events is not supported by evidence.	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid lowering therapy. The committee were therefore unable to update the recommendation on initial therapy. We will pass your comment to the NICE surveillance team which monitor key events relevant to the guideline

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Sanofi	Guideline	006 – 007	026 – 004	The section on escalation of therapy is not helpful. It simply directs to the individual NICE TA's for the "other therapy options" and offers no guidance on escalation or sequence of therapy. It would help clinicians if reference to the National Lipid management pathway was included?	Thank you for your comment. The scope of this update did not cover providing a treatment pathway. The guideline is unable to cross refer to guidance not produced by NICE. We will pass your comment to the NICE surveillance team which monitor key events relevant to the guideline.
Sanofi	Guideline	007	005 - 007	Section 1.6.11 – recommendation to consider ezetimibe even if the lipid target is achieved? This statement is only explained by reading the section on why the committee made their recommendations (page 011, line 006) – therefore, it may be prudent to include an explanation here for clinicians to state why ezetimibe can be added even if the target is achieved in certain patients (which ones?) where additional risk lowering is desirable (e.g. as in 2019 ESC/EAS guidelines where LDL-C target is lowered to 1.0 for recurrent event patients).	Thank you for your comment. We have edited recommendation 1.7.11 to make it clear that ezetimibe could be considered to reduce CVD risk further. This would depend on several factors and would be discussed as part of shared decision making with the person.
Sanofi	Guideline	009	010 - 011	We disagree with the comment "Modest reductions in major adverse cardiovascular events such as myocardial infarction, stroke and related deaths were also seen for all 4 medicines". Which 4 medicines does this statement refer to? The current patient level analysis pooled data from ORION9/10/11 assessed the non-adjudicated cardiovascular benefit of inclisiran as part of a safety analysis using standard MedDRA classification and was not powered to show significance (Ray et al, European Heart Journal (2023) 44, 129–138). These findings await	Thank you for your comment. This refers to alirocumab, evolocumab, ezetimibe and inclisiran as listed in the previous paragraph. The committee acknowledge that the data from the ORION trials for major adverse cardiovascular events was an exploratory endpoint based on non-adjudicated terms, and this was discussed when assessing the evidence. A more detailed write up of the committee's discussion of the evidence is available in Evidence Review D. "There was no clinically important difference between inclisiran and placebo in terms of MACE (definition including non-adjudicated events: CV death, cardiac

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				confirmation in the larger CV outcomes trials of longer duration.	arrest, non-fatal myocardial infarction and non-fatal stroke), but the committee agreed that the size of the absolute benefit of inclisiran was encouraging considering that the MACE outcome was exploratory and so the trials were not powered to detect a difference. They agreed that this exploratory endpoint gives indicative evidence that supports the likely translation of decreased cholesterol levels to reduced cardiovascular events, and they had confidence in the findings as being sufficient to inform the economic model."
Sanofi	Guideline	009	016 - 025	We have some concerns that CV risk is diluted in the model. The model estimates the baseline risk by the cholesterol level of the patients, and although the dataset of patients used have various underlying conditions that may increase risk, in those patients with the highest risk the impact of these risk factors might have been diluted in the analysis. A patient with a single episode of stable angina resulting from a single coronary lesion will not have the same CV risk as a recurrent event polyvascular patient with other risk factors such as diabetes/familial hypercholesterolaemia/chronic kidney disease/inflammatory disease. In the ESC/EAS 2019 guidelines this group of patients with atherosclerotic cardiovascular disease who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin	Thank you for your comment. You are right that the model looks at the entire population and not specifically at a higher risk population with comorbidities and/or multiple events. We do not know if a lower target would be cost-effective for these patients. We cannot be sure that the relationship between cholesterol reduction and cardiovascular outcomes, as measured by the CTTC, is the same as for the population as a whole and the gain in life expectancy could be less given their additional risk factors. We have added this to the limitations section of the model report and added a paragraph on 'People at very high risk' to the 'Committee discussion of the evidence' in Evidence Review D.

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				therapy, an LDL-C goal of < 1.0 mmol/L has been considered.	
Sanofi	Guideline	009	029	We refute the comment that PCSK9 inhibitors are only slightly more effective than inclisiran. While there are no head-to-head studies early real world data is showing lower % LDL-C reductions than seen in the inclisiran trials with high interindividual variation (Makhmudova et al, Clinical Research in Cardiology https://doi.org/10.1007/s00392-023-02247-8). We do not yet know if patients will be more adherent to this therapy (since they may not come back for the second injection), while we can monitor surrogates for PCSK9i adherence through our Homecare service. Furthermore, it may be prudent to consider carrying out a meta-analysis to assess area under the curve for LDL-C owing to the different pharmacokinetics of LDL-C reductions over time on both treatments (time-averaged LDL-C reduction).	Thank you for your comment. The statement that PCSK9 inhibitors are only slightly more effective was based on our original network meta-analysis of LDL-C and non-HDL-C outcome data from all available randomised trials that met the review protocol. This estimated a mean difference in % reduction in LDL-C compared with baseline statin treatment alone of -51.27 (95%CI: -61.88, -40.52)% for inclisiran and -55.01 (95%CI -60.33, -49.39)% for PCSK9 inhibitors. Thank you for highlighting the real-world study you cited. The review protocol for this update specified that only randomised trial data would be included as this provides the most robust source of data for comparing interventions. Furthermore, the clinical review protocol excluded statin intolerant populations and so this study was not eligible for inclusion. We acknowledge there is some uncertainty about adherence. This is why we conducted sensitivity analyses around adherence to both ezetimibe and inclisiran. It is not known how the area under the curve (AUC) analysis relates to CVD risk reduction because it has not been routinely measured/reported for the main endpoint trials.

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Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	005	005 – 007	1.6.1 agree that an absolute target value for non-HDL is preferable to a % reduction from baseline. However, introducing a different value, based on cost-effectiveness rather than clinical efficacy, is inappropriate and confusing and I'd recommend sticking to the targets in AHSN, AAC and JBS3 of non-HDL <2.5 (LDL <1.8)	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	006	019	1.6.6 This should be a "consider" trying lower intensity statin. At this point, if the patient is on a less than max dose of high intensity statin, adding in ezetimibe, or injectable therapy if targets are met, may be preferable. We also suggest adding to this list; Consider trialling a high intensity statin at alternate day dosing (in line with AAC statin intolerance pathway 2020) with daily Ezetimibe.	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid lowering therapy. and the committee were therefore only able to make minor wording changes to this recommendation.

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Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	006	027 – 029	1.6.9 We think this should be: If non-HDL is not <2.5 then assess LDL: If LDL 1.8 – 2.5 add Ezetimibe. If LDL ≥ 2.6 offer injectables.	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	007	001 – 004	1.6.10 as per 1.6.9 comment above	Thank you for your comment.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	007	005 - 007	1.6.11 We suggest this would be much simpler if patients were put on statin plus Ezetimibe from the start	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid modification therapy. The committee is therefore unable to make a recommendation on initial therapy.
Sheffield Teaching Hospitals NHS	Guideline	007	009 - 013	1.6.12 We disagree that Ezetimibe monotherapy should be considered when patients can achieve much lower LDL-C results with injectables or Nustendi, favouring PSCK9i at present (if targets met) due to clinical outcome data. In addition, there is no evidence that Ezetimibe	Thank you for your comment. The committee did not review the evidence on statin intolerance and referred to the technology appraisals on the relevant treatment options. The TAs on PSCK9i recommends them

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Foundation Trust				monotherapy improves cardiovascular outcomes. Evidence for clinical efficacy comes from trials when combined with statin therapy, where it has been shown to provide a greater additional LDL-lowering effect compared to that achieved by monotherapy, due to synergy between statin/ezetimibe mechanisms of action. Again we would suggest; If LDL 1.8 – 2.5 add Bempedoic Acid and Ezetimibe. If LDL ≥ 2.6 offer injectables, favouring PCSK9i if targets are met.	'despite maximal tolerated lipid-lowering therapy'. Similarly, the TA on inclisiran states that: low-density lipoprotein cholesterol (LDL-C) concentrations are persistently 2.6 mmol/l or more, despite maximum tolerated lipid-lowering therapy, that is: • maximum tolerated statins with or without other lipid-lowering therapies or • other lipid-lowering therapies when statins are not tolerated or are contraindicated.
Surrey Heartlands Health and Care Partnership	Guideline	005	004 – 007	Draft guideline targets are different to current QOF indicator targets (CHOL002). The two should be aligned. Personal preference: LDL-C ≤ 1.8mmol/ml. Please consider alignment to the lower target as this would bring us into closer alignment with our European guideline colleagues, cause less confusion for our primary care colleagues and further reduce CVD risk in an already high risk CVD patient population.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator.

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Surrey Heartlands Health and Care Partnership	Guideline	006	024 – 025	I think that this comment should be given more context to make it clear to patients that the greatest reduction in CVD risk is achieved when using high intensity statins at their highest tolerated doses licensed for a particular condition.	Thank you for your comment. The committee agree but wanted to reinforce the benefit of taking any statin in this recommendation. Recommendation 1.7.2 recommends atorvastatin 80mg to people with CVD.
Surrey Heartlands Health and Care Partnership	Guideline	007	005 - 007	Greater clarity required as to in what scenarios/patient groups/supporting rationale, when an HCP should consider ezetimibe if the lipid target is met or exceeded. If the lipid target has been met then what else is the HCP/patient working towards?	Thank you for your comment. The evidence showed (see evidence review D) that ezetimibe was cost effective regardless of the person's lipid levels, the committee therefore decided that it could be considered for people with lipid levels below the agreed targets of 2.0 mmol/litre for LDL cholesterol and 2.6 mmol/litre for non-HDL cholesterol, taking into account the trade-off between increasing medication (the committee noted that a combination pill of atorvastatin and ezetimibe is available in the USA), minimising risk and the burden of implementation which is most likely to fall within primary care. We have edited recommendation 1.7.11 to make it clear that ezetimibe could be considered to reduce CVD risk further. This would depend on several factors and would be discussed as part of shared decision making with the person.
UK Clinical Pharmacy Association: Cardiovascular Committee	Guideline	005	004 – 007	**Target levels –** very confusing and completely disagree with these targets. We need to remember that Low Density Lipoprotein-Cholesterol (LDL-C)is calculated and therefore is dependent on which equation we use and there will always be some variation with the same reading if repeated twice within very short period. We should stick	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY

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				to European Society of Cardiology / Quality Outcomes Framework and national lipid pathway target <1.8 mmol/ litre LDL-C. **It is not correct to say that non-High Density Lipoprotein-Cholesterol (non-HDL-C) of 2.6mmol/litre is equivalent to LDL-C of 2.0 mmol/litre. Here are some examples of non-HDL-C of 2.6mmol/litre variations in LDL-C and why converting LDL-C to non-HDL-C is not correct.** -Total Cholesterol (TC) = 3.6, High Density Lipoprotein (HDL)=1, Triglycerides (TG)=1.7, Low Density Lipoprotein (LDL)=1.8 is non-HDL-C of 2.6 -TC = 3.6, HDL=1, TG=1.5, LDL=1.9 is non-HDL-C of 2.6 -TC = 3.6, HDL=1, TG=1.9, LDL=1.7 is non-HDL-C of 2.6 We should stick with non-HDL-C <2.5mmol/litre and leave it at that. This is very confusing.	benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. The committee were aware that there is no exact equivalent non-HDL level for a specific LDL level and vice versa. However, they both represent a continuum of cardiovascular risk. They decided that there should be a non-HDL target in addition to the LDL target. The committee discussed using equations such as the Friedewald and Sampson but due to their potential limitations, for example the former has not be validated in a statin treated population, preferred to use the distributions from the CPRD dataset, where a 2.0 LDL cholesterol equivalent target that would lead to the same proportion (42%) of people escalating would be 2.6 non-HDL cholesterol. An alternative approach would be to use the Friedewald equation and insert the mean triglyceride level of 1.4 mmol per Litre along with

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					the LDL cholesterol of 2.0 mmol per litre. This approach also indicates a non-HDL cholesterol target of 2.6 mmol per litre.
UK Clinical Pharmacy Association: Cardiovascular Committee	Guideline	005	004 – 007	This is not correct. LDL-C cannot be calculated if non-HDL-C is not recorded. Most labs do not measure LDL-C but calculate it using an equation (such as the Friedewald equation) using HDL-cholesterol as one of the parameters in the calculation. So, if there is no record of non-HDL-cholesterol, it is unlikely there'd be an LDL-cholesterol value.	Thank you for your comment. Recommendation 1.7.1 has been edited to refer to a target for either LDL or non-HDL.
UK Clinical Pharmacy Association: Cardiovascular Committee	Guideline	005	010 – 016	There should be an option of an alternative statin, not just lowering the dose. Interaction or side effects or preference might be met by offering an alternative statin. There is no mention of using an alternative statin i.e. rosuvastatin. There needs to be clarity around what constitutes "patient preference" and clarification whether this will happen after discussion with the patient so they can make an informed decision. Furthermore, there needs to be consideration of offering an alternative statin first, rather than a reduced dose of atorvastatin.	Thank you for your comment. The evidence for this recommendation was not reviewed as part of this update and therefore only minor changes in wording could be made by the committee. Recommendation 1.7.3 has been edited and now states if the person would prefer to take a lower dose. Recommendation 1.9.2 includes changing to a different statin in the same intensity group (rosuvastatin if already receiving atorvastatin).
UK Clinical Pharmacy Association: Cardiovascular Committee	Guideline	006	013 – 020	There is no mention of differential diagnosis as per national statin intolerance pathway. No discussion around assessment for potential other causes of reports of side effects to statins (measure creatinine kinase (CK), vitamin D, thyroid function etc).	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid lowering therapy. The committee were therefore unable to make recommendations on differential

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					diagnosis or the assessment for potential other causes of reports of side effects of statins.
UK Clinical Pharmacy Association: Cardiovascular Committee	Guideline	007	005 - 007	This recommendation will be very confusing to patients and clinicians. Albeit ezetimibe demonstrates reductions at any lipid level, it will be very difficult to explain to patients why another medication is needed although they have met the target by taking their statin. It will also raise the question whether a further lipid target should be set and what that will be. Moreover, the proposed indicator does not provide an impetus for primary care to provide further lipid management for those who have already achieved the lipid target so this recommendation is not likely to be actioned as resources are limited.	Thank you for your comment. The evidence showed (see evidence review D) that ezetimibe was cost effective regardless of the person's lipid levels, the committee therefore decided that it could be considered for people with lipid levels below the agreed targets of 2.0 mmol/litre for LDL cholesterol and 2.6 mmol/litre for non-HDL cholesterol, taking into account the trade-off between increasing medication (the committee noted that a combination pill of Atorvastatin and ezetimibe is available in the USA), minimising risk and the burden of implementation which is most likely to fall within primary care. We have edited recommendation 1.7.11 to make it clear that ezetimibe should be considered to reduce CVD risk further. This would depend on several factors and would be discussed as part of shared decision making with the person.
UK Clinical Pharmacy Association: Cardiovascular Committee	Guideline	007	014 - 018	There needs to be consideration of the possibility of ezetimibe intolerance. Perhaps this could make clear whether or not it is recommending bempedoic acid as sole therapy when neither statin nor ezetimibe are tolerated. The evidence for use of bempedoic acid in this way has moved on since the NICE technology appraisal (TA) for bempedoic acid.	Thank you for your comment. Recommendation 1.10.2 now refers to the technology appraisals including TA694 on bempedoic acid. As the evidence was not reviewed for this recommendation but was based on the technology appraisal the committee were unable to make recommendations on ezetimibe intolerance because it was not covered in these.

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UK Clinical Pharmacy Association: Cardiovascular Committee	Guideline	007	019 - 023	Seems strange to recommend measuring TG only after starting statin treatment and even then, not recommending a fasted blood test ever.	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid lowering therapy and therefore the committee were unable to make recommendations on blood tests at the start of treatment. Recommendation 1.11.1 has been edited and now recommends a full lipid profile which could be non-fasted or fasted.
UK Clinical Pharmacy Association: Cardiovascular Committee	Guideline	007	028 - 029	An annual non HDL-C measurement is not in line with the national lipid pathway and clinical practice. I would always recommend annual full lipid profile, including LDL-C. Disagree with just annual non-HDL-C. We should order an annual non-fasting full lipid profile, not just non-HDL-C. TG make a difference. This is not in line with good practice in reviewing lipid management. This is contradicting the national lipid pathway which recommends non-fasting full lipid profile.	Thank you for your comment. Recommendation 1.11.9 has been edited and now recommends a full lipid profile which includes triglycerides. The test could be non-fasted or fasted.
UK Clinical Pharmacy Association: Cardiovascular Committee	Guideline	010	017 - 019	Talks about non-HDL-C 2.6 mmol/litre being roughly equivalent to LDL-C 2mmol/litre, but we know that to be unreliable depending on TG. We should not be converting LDL-C to non-HDL-C. This is not right.	Thank you for your comment. The committee discussed using equations such as the Friedewald and Sampson but due to their potential limitations, for example the former has not be validated in a statin treated population, preferred to use the distributions from the CPRD dataset, where a 2.0 LDL cholesterol equivalent target that would lead to the same proportion (42%) of people escalating would be 2.6 non-HDL cholesterol.

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UK Clinical Pharmacy Association: Cardiovascular Committee	Guideline	010	024 - 026	Completely dismissing the importance of a fasting sample is simply not scientific or in line with clinical practice.	Thank you for your comment. Recommendations 1.11.1 and 1.11.9 now refer to a full lipid profile which could be non-fasted or fasted.
UK Clinical Pharmacy Association: Cardiovascular Committee	Guideline	General	General	**Triglycerides are generally neglected in this update.** There is a whole section in the lipid national pathway about triglycerides. This is based on TA805 and clinical guideline (CG)181. TG are important in many areas in this update. Thre seems to be no consideration of TG values when (i) assessing risk and (ii) when interpreting pre-treatment total and non-HDL cholesterol measurements.	Thank you for your comment. The scope of this guidance was to determine thresholds for secondary prevention. While triglycerides and triglyceride-rich lipoproteins are increasingly considered as potentially important in CVD risk, their evidence base is not as well established as for LDL-C. We do not have robust data showing that lowering of TGs improves CVD outcomes and therefore there is no data to make a threshold decision. The REDUCE IT trial improved outcomes in people with HTG, but the benefit was irrespective of starting TG or achieved TG levels. Nonetheless. we do emphasise measuring a full lipid profile and TG level - compared to prior guidance - to allow clinicians to monitor TGs.
University Hospitals Birmingham	Guideline	005	010	1.6.1. The LDL target of < 2.0 mmol/L is higher than previously recommended in NHS England national guidance and it is also higher than international guidelines (eg. AHA, ESC) that recommend either < 1.8 mmol/L or < 1.4 mmol/L. Introducing this new cutoff of < 2.0 mmol will be confusing as it will conflict with other UK recommendations and local guidelines. It is unclear In the justification of the 2.0 mmol/L cutoff exactly which treatments are being used and in which order (although	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. Cost effectiveness has not been considered by other guidelines. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD

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				there is a brief description of this). In particular, it is unclear whether this cutoff is proposed for when to introduce inclisiran to escalate LDL lowering treatment in patients treated with statin and ezetimibe. A target of < 1.8 mmol/L or < 1.4 mmol/L are more widely accepted than 2.0 mmol/L and would be preferable.	to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. The recommendation to offer ezetimibe plus a statin has been removed to avoid any potential conflict with the relevant NICE technology appraisals and to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
University Hospitals Birmingham	Guideline	007	001	1.6.11 This is ambiguous as it implies that you should use inclisiran and mAb PCSK9 inhibitors to achieve the target. In practice most patients that do not achieve their LDL target are not eligible for these medications (eg their LDL is between 1.8 mmol/L and 2.6 mmol/L). This should	Thank you for your comment. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the

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				make it clearer that these medications are only recommended based on the LDL cutoffs in the TAs rather than on the basis of the LDL target if this is the case.	treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs.
University Hospitals Birmingham	Guideline	007	014	1.6.12 The addition of ezetimibe regardless of LDL is reasonable on the basis that it is low cost, safe and clinical trials showing its benefit have not necessarily been based on LDL targets.	Thank you for your comment.
University Hospitals Birmingham	Guideline	007	028	1.6.15 The majority of evidence worldwide is now based on LDL rather than non-HDL. It would be preferable to refer to LDL throughout and it causes confusion to interchangeably refer to LDL and non-HDL. The use of both of these measures will make this guideline difficult to implement from a practical perspective.	Thank you for your comment. Non-HDL has been given as LDL may not always be recorded or requested.
University Hospitals Sussex NHS Foundation Trust	Guideline	005	005	1.6.1 – nonHDL and LDL target. I think this would be a significant challenge to implement. Firstly it is different from the targets we have been using for years (LDL <1.8 in secondary prevention) and those already in ESC/EAS, NHSE/AAC, national stroke and JBS guidelines (and QOF). It would be significantly difficult to get all those guidelines changed and all the local pathways which have used these figures to guide treatment escalation. It also goes against the increasing evidence suggesting that the higher the risk the lower the LDL target should be and therefore all education in regards to the existing guideline around targets encourages people to treat to at least <1.8 but preferably lower and there would be no appetite to re-educate everyone based on a poorer target which lacks evidence and result in unnecessary mortality and	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. Cost effectiveness has not been considered by other guidelines. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England

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				morbidity due to us undertreating our patients. It is also odd as the NICE TAG for Inclisiran suggest anyone with an LDL or 2.6 and above would get cost effective and clinical effective benefit from the drug and this will take the person to an LDL of 1.3 mmol/L. If we are recommending treating people to reach a target of <1.4 (which is also another target widely published in guidance and where we would hope the new NICE guidelines proposed) then it is challenging to say you only need people to be treated to <2.0 mmol/L. This will be a back step in all the hard work we have been undertaking encouraging people to take up the newer therapies and that lipid reduction is important. Given that we know we are undertreating people, CVD is the biggest killer in the world, has a bigger effect in women and those with social deprivation we would propose that LDL target should be better than historic guidelines and to propose <1.4 mmol/L in line with the149xcelent NICE TAG or Inclisran for example and underline the vital importance of significant LDL reduction. The LDL receptor works optimally between the concentrations of about 0.6-1.8 mmol/L therefore if we reduce LDL to <1.8 we have only rendered it into the normal physiological range therefore ideally we should be pushing for LDLs<1.0 but 1.4 seems to be a challenging and inspirational target which should result in lives saved. <2.0 is a back step and out of keeping with all other guidelines.	to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. Recommendation 1.7.11 recommends that ezetimibe can be considered to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is achieved.

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University Hospitals Sussex NHS Foundation Trust	Guideline	006	027	1.6.9 We applaud the recommendation of ezetimibe. Given the lost cost and efficacy and the additional time and appointments and blood tests needed to titrate drugs up in a step wise fashion can we consider moving this up and suggesting all secondary prevention patients are started on Atorva 80 and Ezetimibe 10 mg immediately? We know pt concordance is improved if all drugs started at the time of the event, we know people are lost to follow up or there is no follow up in some locations. We know there is a huge burden on phlebotomy and pathology services for blood tests and clinician time to review. This seems to be an excellent opportunity to save resource, time and money and improve pt outcomes but removing an unnecessary step and doing both drugs immediately. Particularly if we are going to ask for excellent LDL control, not moderate control. This would be low cost and high impact and be a cost saving for NHS resources and pt time. It also reduces the delay in getting the patient to target. We can see 1.6.11 you suggest ezetimibe irrespective of injectable therapy which is an excellent recommendation but by placing it at 1.6.9 you suggest you do it first, then consider the injectables (which seems sensible based on price and resource) and therefore 1.6.11 is less relevant but it is good to be clear that there is benefit at any LDL (which argues we should have a lower target than the LDL of 2.0 as this is contradictory to the high target above).	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to make it clear that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid modification therapy. The committee were therefore unable to make recommendations on initial treatments, only on escalating treatments in relation to the target.

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University Hospitals Sussex NHS Foundation Trust	Guideline	007	028	1.6.25 – the importance of picking up post prandial hypertriglyceridaemia is important but there is now an issue with the NICE TAG for icosapent ethyl (ICPE). ICPE is missing from this guideline. This is a lipid/risk modification guideline and therefore we should consider all apoB particles not just LDL. The current NICE TAG says consider ICPE when LDL is <2.6 and trig >1.7 – importantly 'fasting triglycerides'. Although there in no need to prove the triglyceride reduction this is a lipid lowering drug but in this respect a CVD risk reducing drug. It is important to consider it in both the statin and statin intolerant drug lists with the PCSK medications (and bempedoic acid). Could you say 'Consider an annual non-fasting blood test for non-HDL cholesterol to inform discussion and if LDL is 2.6 mmol/L or lower and triglyceride 2.0 mmol/L or higher consider a fasting lipid test to assess eligibility for icosa pentethyl.' It is just the NICE TAG is clear the eligibility criteria is based on having a fasting lipid which is somewhat against the understandable stance that non-fasting lipids are more predictive or risk. How important do you think the risk assessment is though in this cohort as they are already established as high risk, all the drug indications are based on LDL (which is calculated on fasting lipid profiles) or need fasting lipid profiles? Could you suggest that 'as patient is already established as high risk fasting lipid profiles may be more practical to assess lipid criteria for medication escalation' and then something about non-	Thank you for your comment. The recommendations consulted on form part of the guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification. Recommendations 1.12.5 - 1.12.7 (on omega 3 fatty acid compounds, and on combination therapy) in that guideline include reference to icosapent ethyl in line with TA805. The guideline now included a full lipid profile which includes triglycerides in recommendation 1.11.9. The test can be fasted or non-fasted and therefore could include LDL if required.

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				fasting not changing lipid profiles in most people and are better at establishing risk? It is clear why you suggest non-fasting but in reality people won't be able to asses eligibility for the injectables and ICPE if they don't have an LDL or a fasting trig.	
University Hospitals Sussex NHS Foundation Trust	Guideline	010	008	Apologies for confusion. If taking ezetimibe in addition at any LDL value is cost effective and no one is eligible for injectable for an LDL or 2.5 or below when what is the relevance of the cost effectiveness analysis at 2.2 versus the target of 2.0? I think the target encourages people to use more than one agent e.g. statin and ezetimibe, to encourage lifestyle modification etc. The target and the treatment thresholds are different and we already can't treat anyone (assuming we start everyone with atora and ezetimibe) with an LDL or 2.2 or 2.3 etc with anything else anyway. Therefore it is questionable why the cost effectiveness should affect the target, it is more applicable for when to add in the other drugs and that is already found in the NICE TAGs. We don't want people to stop therapy as they have undershot the target for example and think they are being excessive.	Thank you for your comment. It has been assumed that injectables could be prescribed so that a patient can meet the cholesterol target, even if they are below the treatment threshold for the injectable stated in the relevant TA (e.g. 2.6 mmol/litre LDL-C for inclisiran). For this reason, cost effectiveness is a key consideration.
University Hospitals Sussex NHS Foundation Trust	Guideline	011	002	It is unclear the rationale for saying some people with LDL between 2.0 and 3.1 will not get extra treatments if we give them ezetimibe at onset of event. Is this about Inclisiran? Anyone with and LDL of 2.5 and below won't be eligible. LDL of 4/3.5 is the criteria for alirocumab and evolcumab. Effectively render some people beneath the LDL target of PCSK9i (but then they may still be eligible	Thank you for your comment. We agree that this part of the rationale was unclear, and the paragraph has now been deleted. The committee have decided that a lower target would be a fairer and more effective recommendation than ezetimibe for all and a higher cholesterol target.

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				for Inclisiran) but then some beneath the Inclisiran threshold. However we have outcome and long term safety data for ezetimibe so why are we trying to ensure pts can get the expensive injectables by not using ezetimibe? Most people in reality will be beneath all the injectable targets in reality and given some areas are refusing to give Inclisiran and the environmental impact of the pen devices why are we trying to ensure that the most people possible are eligible for injectables? Is this because we believe that significant LDL reduction is important (which of course it is) and we want their LDLs as low as possible, which is all true. There is just cost and resource issues with the injectables with lipid clinics overwhelmed despite lack of referrals for PCSK9i and some areas not giving Inclisiran at all.	
West Yorkshire Integrated Care Board - Lipid Optimisation Clinical Taskforce.	Guideline	007	005 - 024	Consider adding ezetimibe in addition even if target reached. Why? In which patients? Annual non HDL, I would always recommend annual full lipid profile, including LDL No mention of triglycerides in the entire document.	Thank you for your comment. The committee have clarified in recommendation 1.7.11 that this is to reduce CVD risk further. The scope of this guidance was to determine thresholds for secondary prevention. While triglycerides (TGs) and triglyceride-rich lipoproteins (TRLs) are increasingly considered as potentially important in CVD risk, their evidence base is not as well established as for LDL-C. We do not have robust data showing that lowering of TGs improves CVD outcomes and therefore there is no data to make a threshold decision. The REDUCE IT trial improved outcomes in people with HTG, but the

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					benefit was irrespective of starting TG or achieved TG levels. Nonetheless. we do emphasise measuring a full lipid profile and TG level - compared to prior guidance - to allow clinicians to monitor TGs. The committee have edited recommendation 1,11,9 which now recommends offering a full lipid profile.
West Yorkshire Integrated Care Board - Lipid Optimisation Clinical Taskforce.	Guideline	007	014	Perhaps this could make clear whether or not it is recommending bempedoic acid as sole therapy when neither statin nor ezetimibe tolerated. The evidence for use of bempedoic acid in this way has moved on since the NICE TA for bempedoic acid. As usual for NICE they have swerved consideration of triglyceride values when (i) assessing risk and (ii) when interpreting pre-treatment total and non-HDL-cholesterol measurements.	Thank you for your comment. Recommendation 1.10.2 now refers to the technology appraisals including TA694 on bempedoic acid. The scope of this guidance was to determine LDL thresholds for secondary prevention. While triglycerides (TGs) and triglyceride-rich lipoproteins are increasingly considered as potentially important in CVD risk, their evidence base is not as well established as for LDL-C. We do not have robust data showing that lowering of TGs improves CVD outcomes and therefore there is no data to make a threshold decision. The REDUCE IT trial improved outcomes in people with high TGs, but the benefit was irrespective of starting TG or achieved TG levels. Nonetheless. we do emphasise measuring a full lipid profile and TG level - compared to prior guidance - to allow clinicians to monitor TGs.

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West Yorkshire Integrated Care Board - Lipid Optimisation Clinical Taskforce.	Guideline	007	019	We need baseline monitoring, include full lipid profile, TGs, HbA1c, TFTs, LFTs etc. all needs to be in line with what we have been educating clinicians. Please see national lipid pathway.	Thank you for your comment. Recommendation 1.11.1 has been edited and now recommends a full lipid profile.
West Yorkshire Integrated Care Board - Lipid Optimisation Clinical Taskforce.	Guideline	007	020	seems strange to recommend measuring TGs only after starting statin treatment ad even then not recommending a fasted blood test.	Thank you for your comment. The scope of the guideline update specified that the following would be updated: Follow-up of people started on statin treatment and the secondary prevention: escalation of lipid lowering therapy and therefore the committee were unable to make recommendations on blood tests at the start of treatment. Recommendation 1.11.1 has been edited and now recommends a full lipid profile which could be non-fasted or fasted.
West Yorkshire Integrated Care Board - Lipid Optimisation Clinical Taskforce.	Guideline	007	028	Annual monitoring should be of non-fasting FULL lipid profile. Triglycerides are not mentioned sufficiently enough in the document and should be mentioned earlier. The measurements must include trigs to properly understand the CVD risk, as the non-HDL contains many elements in addition to LDL cholesterol. The evidence shows that non-HDL-c becomes less reliable and relevant when TG >5.6. All translations of LDL-C values to non-HDL-C assume a very low TG. If TGs are high, then the	Thank you for your comment. The scope of this guidance was to determine thresholds for secondary prevention. While triglycerides and triglyceride-rich lipoproteins are increasingly considered as potentially important in CVD risk, their evidence base is not as well established as for LDL-C. We do not have robust data showing that lowering of TGs improves CVD outcomes and therefore there is no data to make a threshold decision. The REDUCE IT trial improved outcomes in people with HTG, but the benefit was irrespective of starting TG or achieved TG levels.

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				estimation of LDL-C from non-HDL-c becomes completely inaccurate.	Nonetheless. we do emphasise measuring a full lipid profile and TG level - compared to prior guidance - to allow clinicians to monitor TGs.
West Yorkshire Integrated Care Board - Lipid Optimisation Clinical Taskforce.	Guideline	009	028	Comparison of inclisiran and PCSK9i, but the missing cardiac outcome data for inclisiran not mentioned.	Thank you for your comment. Evidence for major adverse cardiac events for participants taking inclisiran was available from the ORION 10 and 11 trials, although the committee acknowledge that the ongoing ORION 4 trial has not yet reported. In ORION 10 and 11, although the cardiovascular endpoint was exploratory based on non-adjudicated terms, the committee had confidence in the findings as being sufficient to inform the model and to support the likely translation of decreased cholesterol levels to reduced cardiovascular events. This is outlined in the write up of the 'Committee Discussion of the Evidence'.
West Yorkshire Integrated Care Board - Lipid Optimisation Clinical Taskforce.	Guideline	010	012	still don't understand why they've gone for 2mmol/L rather than 1.8!	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has

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					been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator.
West Yorkshire Integrated Care Board - Lipid Optimisation Clinical Taskforce.	Guideline	010	017 - 025	Talks about non-HDL 2.6 being roughly equivalent to LDL 2, but we know that to be unreliable depending on TGs Says non-HDL preferable to LDL as fasting sample not needed. But I disagree.	Thank you for your comment. The committee discussed using equations such as the Friedewald and Sampson but due to their potential limitations, for example the former has not be validated in a statin treated population, preferred to use the distributions from the CPRD dataset, where a 2.0 LDL cholesterol equivalent target that would lead to the same proportion (42%) of people escalating would be 2.6 non-HDL cholesterol. Recommendations 1.11.1 and 1.11.9 now refer to a full lipid profile which could be non-fasted or fasted.
West Yorkshire Integrated Care Board – Lipid Optimisation Clinical Taskforce.	Guideline	005	004 – 007	We welcome the recommendation to have a numerical target for lipid levels. However, there are a few problems here. Firstly, it is extremely concerning that the proposals in this draft guidance are for higher levels of LDL/non-HDL than the current targets in the AAC Lipid Pathway which is adopted into clinical practice through the Quality and Outcome Framework. These new targets will create a huge confusion. We have worked hard over 3-4 years to provide consistency in lipid management targets. This is going to undo a lot of hard work. Secondly, we disagree that non-HDL-c is equivalent to a certain LDL-C level. We should stick to recommending an LDL-C <1.8 and non-	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee

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				HDL-c <2.5. These are NOT always equivalent. These are reasonable cut off points. Thirdly, it is important to remember that if non-HDL-c is not available, one cannot calculate LDL-c. There is an assumed low/normal TG of 1.7 in the Friedewald equation to maintain non-HDL-C – LDL-C difference. This is not the same with the Sampson equation. To change from 1.8/2.5 to 2.0/2.6, although trivial, comes across as de-escalation of treatment; instead, the evidence reviewed by NICE should be taken as an endorsement of the existing thresholds we have incorporated into the existing, NICE endorsed AAC national pathway, but with greater emphasis on non-HDL-C unless diagnosing FH or assessing eligibility for TA therapies. The lower the target the more cost savings for the NHS and the better for the health of the nation over all. But lower targets also create greater churn in the system as they are less achievable with only oral medication.	discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. In 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024. The guideline committee discussed using equations such as the Friedewald and Sampson but due to their potential limitations, for example the former has not been formally validated in a statin treated population, preferred to use the distributions from the CPRD dataset, where a 2.0 LDL cholesterol equivalent target that would lead to the same proportion (42%) of people escalating would be 2.6 non-HDL cholesterol. An alternative approach would be to use the Friedewald equation and insert the mean triglyceride level. along with the LDL cholesterol of 2.0 mmol per litre. For this we have used 1.4 mmol per Litre, which is the mean in our dataset at an LDL of 2.0 (rather than assume 1.7 mmol/litre). This approach also indicates a non-HDL cholesterol target of 2.6 mmol per litre.
West Yorkshire Integrated	Guideline	005	001	As we've pointed out before, most labs do not measure LDL-cholesterol but calculate it using an equation (such as the Friedewald equation) using HDL-cholesterol as one	Thank you for your comment. Recommendation 1.7.1 has been edited to refer to a target for either LDL or non-HDL.

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Care Board – Lipid Optimisation Clinical Taskforce.				of the parameters in the calculation. So if there is no record of non-HDL-cholesterol, it is unlikely there'd be an LDL-cholesterol value.	
West Yorkshire Integrated Care Board – Lipid Optimisation Clinical Taskforce.	Guideline	005	005	Using ESC recommendations, we would target LDL <1.8mmol/L and not routinely use non HDL due to issues when TGs high	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. Both LDL and non-HDL have been given in recommendation 1.7.1 allowing for non-HDL to be used in the presence of high triglycerides.
West Yorkshire Integrated Care Board – Lipid Optimisation	Guideline	005	010	No mention of using an alternative statin i.e. rosuvastatin. And what do they mean by patient preference? In what scenario? Is this after a discussion with them so they can make an informed decision? Can they be offered an alternative statin first, rather than a reduced dose of atorvastatin?	Thank you for your comment. Recommendation 1.9.2 recommends rosuvastatin as an option if the person reports adverse events. Patient preference may be a factor if the person is concerned about possible side effects for example. Recommendation 1.7.3 has been edited and now states if the person would prefer to take a lower dose.

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Clinical Taskforce.					
West Yorkshire Integrated Care Board – Lipid Optimisation Clinical Taskforce.	Guideline	006	004 – 025	Need linking to the NICE Approved AAC guidance on statin intolerance and lipid management. Several points are missing. E.g., differential diagnosis, certain terminology "Dechallenge, rechallenge", using once a week / twice a week statin etc.	Thank you for your comment. NICE guidelines are only able to cross-refer to other guidance produced by NICE. The evidence was not reviewed for recommendation 1.9.2 and therefore the committee could only make minor wording changes. The recommendation does cover specific strategies but does not preclude others being tried based on a discussion between the person and the health professional.
West Yorkshire Integrated Care Board – Lipid Optimisation Clinical Taskforce.	Guideline	006	013	No discussion around assessment for alternative diagnosis of reports of side effects to statins (measure Creatine Kinase, vit D, thyroid etc)	Thank you for your comment. The evidence for this recommendation was not reviewed as part of this update and the committee were therefore only able to make minor wording changes. We will pass your comment to the NICE surveillance team which monitor key events relevant to the guideline and for consideration if the guideline is updated.
West Yorkshire Integrated Care Board – Lipid Optimisation Clinical Taskforce.	Guideline	007	001 – 018	The economic report concludes that inclisiran was cost effective above 3.1 mmol/litre of LDL-C. This is not inline with the inclisiran TA. Potential reasons are presented. However, this is not just confusing, it goes to show that the economic model used has a higher LDL-C threshold overall, not just for inclisiran. This could explain what the economic model identified 2.2 LDL-C to be a cost-effective target.	Thank you for your comment. Although in the model the optimal treatment threshold for inclisiran was 3.1 mmol/litre of LDL-C, we have since noted that the net health benefit for a target of 2.6 mmol/litre in the guideline model is actually only slightly lower than that of 3.1 mmol/litre. Therefore, inconsistencies with the TA are not as great as they at first seem.

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				LDL-C lowering only reduces CV deaths not non-CV deaths. It's when CV deaths exceed a certain proportion of all deaths that LDL-C lowering then may offer all-cause mortality benefits. The TA733 model applied a treatment effect to CVD mortality rather than all-cause mortality in the guidelines consultation model. The life-years gained in the TA model were greater because the baseline risk of modifiable CVD mortality was much higher. Figure 1 in the economic report does not reflect the national lipid pathway. I note that later on the report acknowledges that the TA for inclisiran does give the choice between trying ezetimibe or inclisiran. But again, this is all confusing. International guidelines such as ESC indicate that there needs to be at least 50% or more reduction of LDL-C in addition to a target of LDL-C <1.8 or <1.4. This additional condition is to maximise the CV benefit of LDL-C reduction. This is not picked up on in the economic model.	We agree that if we had used the baseline risk of CV outcomes from the TA then we would have reached a lower optimal target. However, there were good reasons for not doing so. In the TA model, CVD mortality was estimated over only one-year, for people who had mostly had a CV event in the last year or two. It was then assumed that the CVD mortality would increase by 5% a year, every year thereafter. Our approach is better because it stratified event rates by age, sex and differentiated between mortality in the prevalent and acute populations. Furthermore, by applying an all-cause mortality treatment effect we avoided problems associated with defining modifiable CVD mortality. We have revised Figure 1 so that it more accurately reflects the national pathway. We acknowledge that not everyone above the target will be escalated to ezetimibe. We have maintained this in the model base case, as this was the most cost-effective pathway. However, we have added sensitivity analyses to the model, where alternative treatment pathways were followed. In two of these analyses, the optimal target remained the same. In a third, the optimal target was slightly higher. The committee decided to stick with the target of 2.0 mmol per litre for LDL cholesterol. The committee decided to focus on recommending a target

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					and do not recommend a treatment sequence for people above the target. The addition of a criteria for a 50% reduction of LDL-C is arbitrary and not based on cost effectiveness. Furthermore, some stakeholders have reported that systems are not set up to record change from baseline. For simplicity, the committee decided not to set a relative reduction target.
Wordsley Green Surgery	Guideline	007	005	1.6.11 Additional add on therapy suggested to use ezetimibe for further optimisation assumingly for LDL target < 1.4. When we look at trial data of this though this may give a 7% RRR of MACE , looking at CV risk reduction these patient with LDL optimised – VAZKEPA is a medication which if eligible may provide much more significant MACE reductions	Thank you for your comment. These recommendations form part of the guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification. That guideline includes recommendations on omega 3 fatty acid compounds, and on combination therapy (1.12.5 – 1.12.7) which include reference to icosapent ethyl in line with NICE TA805.
Wordsley Green Surgery	Guideline	007	009	1.6.12 Offering ezetimibe as blanket second line, may limit the numbers of patient eligible for PSCK9i / Si RNA for example a patient with an LDL of 2.8 given ezetimibe on maximum dose statin – would return with an LDL of 2.5 then bempedoic acid may not return them to an LDL target of 1.8. Consideration should be given for this	Thank you for your comment. The committee did not review the evidence on statin intolerance and referred to the technology appraisals on the relevant treatment options. The TAs on PSCK9i recommends them 'despite maximal tolerated lipid-lowering therapy'.

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Wordsley Green Surgery	Guideline	007	020	1.6.14 I would recommend fasted cholesterol were possible. Rationale is triglyceride variability . LDL is calculated measure not a pure measure so there may be variability there. For medication such as Vazkepa their recommendation is based upon a fasted lipid profile	Thank you for your comment. Recommendation 1.11.1 has been edited and now recommends a full lipid profile which could be non-fasted or fasted.

Respondent	Document	Page No	Line No	Comments	Developer's response
Novartis Pharmaceuticals UK Ltd	Guideline	005	005	Regarding recommendation 1.6.1., we welcome the use of a hard lipid target versus a percentage reduction in non-HDL-C. However, we are concerned that the recommended targets (non-HDL-C <2.6 mmol/L and LDL-C <2.0 mmol/L) will confuse HCPs. In particular, HCPs in primary care and non-lipid specialist secondary care practitioners, who are widely suggested to be the main users of these guidelines, may be confused by the contradictions and inconsistencies between this NICE guidance and the large number of widely used national and international guidelines, and/or clinical pathways, which are consistent with a target LDL-C of 1.8mmol/L with the exception of those that opt to go lower.	Thank you for your comment. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator. Similarly, in 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its

				The following Pathways/Guidelines recommend an LDL-C target of <1.8mmol/L or non-HDL-C target of <2.5mmol/L • NHSE/AAC pathway[1] • AHSN Lipid Optimisation Pathway following an Acute Cardiovascular Event[2] • QOF 2023/2024[3] • UK National Stroke Guideline[4] • JBS3 pathway[5] • CVDPrevent targets[6] • AHA/ACC pathways[7] International Guidelines such as ESC/EAS pathway[7] go even further in recommending an LDL-C target of <1.4mmol/L along with a percentage reduction of at least 50% from baseline. On page 10, line 19 of the Guideline, NICE acknowledges the discrepancy between its recommendation and that of other national and international organisations and justifies this based on NICE's cost-effectiveness analysis. However, this should not be justified by cost effectiveness alone. The rationale for other guidelines using a target of LDL-C <1.8mmol/L and below is based on clinical evidence from	guidance at the time but this is due to be reviewed in 2024. Recommendation 1.7.11 recommends that ezetimibe can be considered to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is achieved. The target is based on both clinical and cost effectiveness. The RCT outcomes on treatment efficacy was used to inform the economic model.

				intravascular ultrasound studies evaluating coronary atherosclerosis. Studies have demonstrated progression of plaque volume can be substantially diminished when LDL-C levels of 1.8mmol/L are achieved; with plaque regression demonstrated at even lower achieved LDL-C values.[8] These studies support the narrative of 'the lower, the better' for LDL-C targeted reduction. In fact, NICE's proposed guidelines on pg. 9, line 3 mention that "*The committee agreed lipid levels should be reduced as much as possible in people with CVD*". However, this is not appropriately reflected in the chosen lipid targets for secondary prevention as it is "*explicitly based on the cost-effectiveness of treatment escalation*". While it is acknowledged that NICE guidance aims to meet the population's needs by identifying care and outcomes within an available budget, the guidance is also expected to be based on evidence-based recommendations. CG181 is expected to be a clinical guideline driven by clinical evidence, as reflected in the document name, therefore, decisions based on cost-effectiveness alone are not justified. • In line with the above, we strongly encourage NICE to consider revising the targets to reflect a non-HDL-C <2.5mmol/L and LDL-C <1.8mmol/L.	

				Notably, the committee had found "*that escalation of treatment was cost-effective for people on statins with LDL- C levels of more than 2.2mmol/litre*" (page 10, line 8), however "*the committee decided to favour 2.0, to allow more people to be treated*" (page 10, line 11). Evidence suggests that lower LDL-C targets correlate with a decreased burden of atherosclerosis and better clinical outcomes for patients.[8] Therefore, a more stringent LDL-C target would be a more pragmatic approach for the committee to consider. The committee noted that the 2.0mmol/L target was higher than other targets but mentioned that they "*thought it was sufficiently similar to mean it was likely to be implemented*" (page 10, line 21). However, research has suggested that when clinical guidelines advocate divergent goals, this results in confusion amongst practitioners, creating clinical inertia[9] and clinical inertia contributes to a widespread failure to achieve evidence-based goals related to lipid control and other clinical domains.[10] Therefore, the discordance of the proposed lipid target in CG181 to the aforementioned national and international guidelines and pathways is likely to reduce NICE guidance implementation rather than increase it. **Reference:**	

				1. NHS, Summary of national guidance for lipid management for primary and secondary prevention of cardiovascular disease, August 2023. https://www.england.nhs.uk/aac/wpcontent/uploads/sites/50/2020/04/lipid-management-pathway-v6.pdf [Accessed September 2023]. 2. The AHSN Network, Lipid Optimisation Pathway following an Acute Cardiovascular Event, Jan 2023. https://www.ahsnnetwork.com/wpcontent/uploads/2023/03/Lipid-Optimisation-Clinical-Pathways-Secondary-prevention-in-primary-care-v546.pdf [Accessed September 2023]. 3. NHSE, Quality and Outcomes Framework guidance for 2023/24, March 2023. https://www.england.nhs.uk/wp-content/uploads/2023/03/PRN00289-quality-and-outcomes-framework-guidance-for-2023-24.pdf [Accessed September 2023] 4. Stroke Association, National Clinical Guideline for Stroke, April 2023, https://www.strokeguideline.org/app/uploads/2023/04/National-Clinical-Guideline-for-Stroke-2023.pdf [Accessed September 2023]	

				5. JBS3 Board, Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3), Heart 2014;100:ii1-ii67. 6. Public Health England, CVDPrevent 2022 New Indicator Guide, https://s3.eu-west-2.amazonaws.com/nhsbn-static/CVDPREVENT/2022/CVDPREVENT%202022%20New%20Indicator%20Guide%20FINAL.pdf [accessed Oct 2023] 7. Mach F. et al, ESC/EAS Guidelines for the management of dyslipidaemias: *Eur. Heart J*, 2019;41(1):111–188. 8. Ference BA et al., Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel: *Eur. Heart J*. 2017;38:2459–2472. 9. Grundy S. et al, 2018 AHA/ACC Guideline on the management of blood cholesterol: *Circulation,* 2019;139:1082-1143. 10. O'Connor PJ, et al., Clinical Inertia and Outpatient Medical Errors. In: Henriksen K, Battles JB, Marks ES, et al., editors. Advances in Patient Safety: From Research to	

				Implementation (Volume 2: Concepts and Methodology). Rockville (MD): Agency for Healthcare Research and Quality (US); Feb 2005. Available from: https://www.ncbi.nlm.nih.gov/books/NBK20513/	
Novartis Pharmaceuticals UK Ltd	Guideline	006	026	We welcome NICE's acknowledgement that the LDL-C lowering effectiveness of ezetimibe vs. placebo and inclisiran vs. placebo are 18% and 51%, respectively (*Economic Analysis Report, Table 12, page 31*). We also welcome NICE's recommendation of a Single Target Approach, albeit the LDL-C target of <2.0 mmol/L contradicts many UK guidelines and pathways, which recommend an LDL-C target of <1.8 mmol/L (*further information on this is provided as a separate comment below*). Notwithstanding the above, we (*and other NHS stakeholders we consulted*) have serious concerns about a substantial number of patients unable to access optimal lipid-lowering therapy, making it more challenging for them to reach NICE's proposed target as an unintended practical consequence of the recommendation wording. This stems from the NICE recommendation wording in TA733, which imposes an LDL-C ≥ 2.6mmol/L threshold before inclisiran can be	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to avoid any potential conflict with the relevant NICE technology appraisals and to make it clearer that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making (including adherence), in accordance with the recommendations in the TAs. The target in this guideline is based on both clinical and cost effectiveness to ensure the optimal allocation of resources for the NHS. The cost per QALY of a target of 1.8 compared to 2.0 LDL-C mmol/L was considerably more than the £20,000 per QALY benchmark used to recommend treatments in this guideline. The cost of getting everyone with CVD to a target of 1.8 mmol/L LDL-C would cost many millions of pounds more and the opportunity cost to other NHS patients would be too great. Information on this has been added to evidence review D and the committee

				used (*Note that the ≥ 2.6mmol/L threshold is not in the inclisiran marketing authorisation*). This is best explained via the following examples: **<u>NICE Proposed Target is LDL-C 2.0 mmol/L and Ezetimibe is Offered to All Patients Before Inclisiran</u>** • **Example 1** – Patients on a high-intensity statin with LDL-C of 2.9mmol/L receive ezetimibe and achieve 18% LDL-C reduction to LDL-C of 2.4mmol/L. These patients may not get to target as they will be unable to access inclisiran since their LDL-C is below 2.6mmol/L • **Example 2** – Patients with LDL-C of 2.6mmol/L receive ezetimibe and achieve 18% LDL-C reduction to LDL-C of 2.1mmol/L. These patients may not get to target as they will be unable to access inclisiran since their LDL-C is below 2.6mmol/L Given that every 1mmol/L reduction in LDL-C translates to a 22% reduction in major adverse cardiovascular events (MACE) (over 5 years)[2], the practical consequence of this recommendation, as currently interpreted by NHS stakeholders, will put patients at risk	discussion of the evidence. The NICE indicator specification will be shared with NHS England to consider alteration to the existing QOF indicator.

				of further CVD events, which is counter to the NICE Guideline's stated ambition. Therefore, we recommend changing the recommendation wording to: • *Offer ezetimibe* ***and/or inclisiran (see the NICE technology appraisal on inclisiran)*** *in addition to the maximum tolerated intensity and dose of statin if the lipid target for secondary prevention of CVD is not achieved.* ***Consideration should be given to offering inclisiran when LDL-C levels are ≥ 2.6mmol/L and ezetimibe when LDL-C levels are < 2.6mmol/L*** This proposed change would result in the NICE proposed Target being attained in the highest number of patients via the lowest combination of therapies possible to maintain adherence, therefore, reducing the risk of CVD events in a substantial number of patients. The examples below illustrate this point: **NICE Proposed Target is LDL-C 2mmol/L and Clinicians have the CHOICE of Ezetimibe and/or Inclisiran** • **Example 1** – Patients with LDL-C of 2.9 mmol/L receive inclisiran and achieve 51% LDL-C	

				reduction to LDL-C of 1.4mmol/L. They will thus meet the NICE Target • **Example 2** – Patients with LDL-C of 3.3 mmol/L receive inclisiran and achieve 51% LDL-C reduction to LDL-C of 1.6 mmol/L. They will thus meet the NICE Target • **Example 3** – Patients with LDL-C of 2.4 mmol/L receive ezetimibe and achieve 18% LDL-C reduction to LDL-C of 2 mmol/L. They will thus meet the NICE Target Finally, it is noteworthy that the committee stated on page 11, line 10 that "*adherence may be lower for people on 2 pills rather than 1*"; this clearly highlights adherence to oral therapy as an issue that could be addressed by an injectable therapy, such as inclisiran, which is HCP administered in **primary care** once every 6 months, on maintenance dose. The DAVINCI study demonstrated that only 30% of patients on high-intensity statin monotherapy and 37% of patients on a combination of a statin with ezetimibe achieved their guideline recommended goal of <1.4mmol/L for	

				secondary prevention patients (based on 2019 ESC/EAS risk-based goal attainment), whereas the utilisation of an injectable therapy combination resulted in 57% of patients attaining guideline-recommended goals.[3] Furthermore, data from the ORION-8 study, a long-term extension study with up to 3 years of follow-up in patients (N=3274) with ASCVD, ASCVD risk equivalent or HeFH who completed either the Phase 2 ORION-3 study or one of the three Phase 3 studies (ORION-9, ORION-10 or ORION-11)[4,] found that 78.4% of patients achieved their pre-specified lipid goals at end of study with inclisiran[5] (pre-specified lipid goals were set at <1.8mmol/L for ASCVD patients and <2.6mmol/L for ASCVD risk equivalents, based on ESC/EAS 2016 goals[6]; data presented at the European Society of Cardiology Congress, 2023). In stark contrast, the CVDPrevent Third Annual report in March 2023 found that only 23.7% of patients, with CVD, had cholesterol levels of non-HDL less than 2.5mmol/l or LDL less than 1.8mmol/l.[7] These data highlight the potential to impact target attainment within England. **Reference** 1. NICE, NICE guideline CG181 Economic analysis report September 2023;	

				https://www.nice.org.uk/guidance/GID-NG10368/documents/economic-report [access Oct 2023] 2. Ference BA et al., Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel: *Eur. Heart J*. 2017;38:2459–2472. 3. Ray KK et al. EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. *Eur J Prev Cardiol*. 2021;28(11):1279-1289. 4. ClinicalTrials.gov. NCT03814187; https://clinicaltrials.gov/ct2/show/NCT03814187 [Access Oct 2023] 5. Wright, RS et al., ORION-8: Long-term efficacy and safety of twice-yearly inclisiran in high cardiovascular risk patients; Presented at ESC Congress Amsterdam 2023. 6. Catapano, AL, et al., Guidelines for the Management of Dyslipidaemias, *Eur. Heart J.* 2016;27:2999-3058 7. CVDPrevent, Third Annual Audit Report, March 2023 https://s3.eu-west-	

				2.amazonaws.com/nhsbn-static/CVDPREVENT/2023/Ref%20376%20CVDPREVENT%20Third%20Annual%20Audit%20Report%20FINAL.pdf [Accessed Oct 2023]	
Novartis Pharmaceuticals UK Ltd	Guideline	006	026	Section 1.6.9 of the Guideline states, "*Offer ezetimibe in addition to the maximum tolerated intensity and dose of statin if the lipid target for secondary prevention of CVD is not achieved.*" The recommendation wording is problematic for several reasons: • First, the ordering of statements 1.6.9 and 1.6.10 reads like a pathway flow to recommend ezetimibe use before inclisiran, which would directly contradict TA733 and the NHS Accelerated Access Collaborative (AAC) pathway. TA733 and the AAC pathway allow for inclisiran use when LDL-C concentrations are persistently 2.6 mmol/l or more, despite maximum tolerated statins with or **without** other lipid-lowering therapies. Novartis has consulted with health care professionals (HCPs) and other NHS stakeholders, and the consensus is that this reads like a pathway.	Thank you for your comment. The recommendation to offer ezetimibe plus a statin has been removed to avoid any potential conflict with the relevant NICE technology appraisals and to make it clearer that we are not recommending a treatment pathway. The committee have simplified recommendation 1.7.10 and it recommends alirocumab, evolocumab, ezetimibe and inclisiran in accordance with the NICE technology appraisals. This is to enable the health professional to discuss the treatment options with the person, as part of shared decision making, in accordance with the recommendations in the TAs. In 2022 NICE confirmed that the NHS Accelerated Access lipid pathway reflected its guidance at the time but this is due to be reviewed in 2024.

				• Second, it appears counterproductive to the NICE Guideline's stated ambition of optimising lipid lowering for secondary prevention of CVD where the risk of further CVD events is greatest as this suggested sequencing (*as is being interpreted by stakeholders*) of lipid lowering therapies will leave some patients unable to reach the proposed target of LDL-C of <2 mmol/L (*Further information on this is provided as a separate comment below*). Given that the economic analysis supporting this Guideline has confirmed that statins, ezetimibe and inclisiran all represent a cost-effective use of NHS resources in primary care, it would be optimal to allow clinicians and patients to have the CHOICE and flexibility of **(a)** statins +/- ezetimibe **(b)** statins +/- inclisiran or **(c)** statins +/- ezetimibe +/- inclisiran. This would also serve to increase treatment adherence over the long term as the treatment combination would be tailored to individual patient preference via shared care decision making; an element which is currently absent from consideration within the proposed guidelines.	

				• Thirdly, polypharmacy is already a challenge for many patients post a CVD event, and the recommendation wording could potentially compound this problem by having patients on 3 treatments for elevated LDL-C, in addition to other medications such as anti-hypertensives, glucose lowering agents and anti-coagulants, all adding to the pill burden and thus reducing the likelihood of long-term compliance. Considering all of these points, we recommend changing the wording of the Guideline recommendation in 1.6.9 to: • *Offer ezetimibe **and/or inclisiran (see the NICE technology appraisal on inclisiran)** in addition to the maximum tolerated intensity and dose of statin if the lipid target for secondary prevention of CVD is not achieved.* An alternative option to avoid perceptions of the Guideline being a pathway would be to include **both** of the following: 1. Include the recommendation wording for both 1.6.9 and 1.6.10, with no separation: i.e. "*Offer*	

				ezetimibe in addition to the maximum tolerated intensity and dose of statin if the lipid target for secondary prevention of CVD is not achieved ***and*** *If the lipid target for secondary prevention of CVD is not achieved (see recommendation 1.6.1), consider alirocumab, evolocumab and inclisiran (see the NICE technology appraisals on inclisiran, evolocumab and alirocumab)*. 2. Explicitly state in the Guideline that this is not guidance on therapy sequencing. The same consideration should be given to the sections covering statin contraindication on page 7 of the draft Guideline: i.e Sections 1.6.12 and 1.6.13 Furthermore, page 1, line 6 of the Guideline states: "*This guideline update introduces a new target for lipid levels for secondary prevention of cardiovascular disease (CVD) and guidance on lipid-lowering treatments other than statins alone to achieve that target*" To avoid confusion, we recommend changing this to • *This guideline update introduces a new target for lipid levels for secondary prevention of*	

				cardiovascular disease (CVD) and guidance on lipid-lowering treatments other than statins alone to achieve that target. ***This guideline is not a pathway or sequencing recommendation****.*	
Novartis Pharmaceuticals UK Ltd	Guideline	010	005	This section states that in the first modelling approach considered by NICE "*the addition of inclisiran was cost effective for people with LDL cholesterol levels of more than 3.1 mmol/litre after treatment with a statin plus ezetimibe*" There are two main issues with this section, and these are taken in turn as follows: **1) <u>This section is confusing and is liable to misinterpretation</u>** The section describes how, having considered two modelling approaches *[(**a**) A Treatment Specific Target Approach and (**b**) A Single Target Approach*], the NICE committee decided to recommend the Single Target Approach with a non-HDL of <2.6 mmol/litre or LDL-C of <2.0 mmol/L. Yet, a lot of the text in this section is devoted to the modelling approach that the	Thank you for your comment. We agree that description of the 3.1 LDL-C treatment threshold for inclisiran in the rationale was potentially confusing. For simplicity, we have removed all reference to that analysis and that threshold from the rationales. It remains in the model report and the detailed committee's discussion section of the evidence report. Although in the model the optimal treatment threshold for inclisiran was 3.1 mmol/litre of LDL-C, we have since noted that the net health benefit for a target of 2.6 mmol/litre in the guideline model is actually only slightly lower than that of 3.1 mmol/litre. Therefore, inconsistencies with the TA are not as great as they at first seem. The committee maintain that the guideline model is evidence-based and robust. It is superior to the TA model in the estimation of mortality. In the TA model, CVD mortality was estimated over only one-year, for people who had mostly had a CV event in the last year or two. It was then assumed that the CVD mortality would increase by 5% a year, every year thereafter.

					Committee rejected, and this has led to confusion amongst various stakeholders over what the guideline actually recommends. Note that we are not aware of any other NICE Guideline in which the development team's deliberations are presented in such a way. It is only by reading the full context in the 99 page economic report accompanying the guideline that it becomes clear that NICE is **NOT** recommending inclisiran for people with LDL-C > 3.1mmol/L, but rather for all people who haven't achieved the LDL-C target of < 2 mmol/L despite ezetimibe therapy. Given the multiplicity of stakeholders involved in implementing NICE guidelines and the need for clarity, we recommend removing all statements referring to 3.1 mmol/L and simply directing the reader to the full economic report for context and details of the Treatment Specific Target Approach considered but NOT recommended by the Committee. For example, page 10, lines 4 to 12 of the guideline could be amended as follows: • *The first approach, **which was subsequently rejected by the NICE Committee**, showed **the treatment***	Our approach is better because it stratified event rates by age, sex and differentiated between mortality in the prevalent and acute populations. Furthermore, by applying an all-cause mortality treatment effect we avoided problems associated with defining modifiable CVD mortality. The utility multipliers were from EQ-5D-3L values using the Health Survey of England, so they represent the most applicable data to a NICE economic evaluation. There was some uncertainty, particularly with non-coronary and coronary revascularisations so different values were tested in the sensitivity analysis: this was found to have no impact on the recommended target. For the cost of CVD events we have used a recent study of CVD patients in a UK population. However, the committee agree that the focus of this guideline update should be on the cholesterol target and not on the treatment sequence. The recommendations and rationales have been adjusted to make this clearer.

				specific targets for escalating therapy as predicted by the model *~~it was cost effective to treat with a statin plus ezetimibe at any lipid level. The addition of inclisiran was cost effective for people with LDL cholesterol levels of more than 3.1 mmol/litre after treatment with a statin plus ezetimibe~~*. ***Full details can be found in the accompanying economic report*** • *The second approach,* ***which was used as the basis for decision-making****, demonstrated that escalation of treatment was cost-effective for people on statins with LDL cholesterol levels of more than 2.2 mmol/litre. There was a little more uncertainty about the cost-effectiveness of escalating treatment for people with LDL cholesterol levels between 2.0 and 2.2. The committee decided to favour 2.0, to allow more people to be treated.* **2) <u>This section contradicts NICE TA733</u>**	

				NICE TA733, published under 2 years ago, found inclisiran cost-effective at LDL-C levels of ≥ 2.6mmol/L. The statement "*the addition of inclisiran was cost-effective for people with LDL cholesterol levels of more than 3.1 mmol/litre after treatment with a statin plus ezetimibe"* directly contradicts TA733 and potentially undermines credibility in the NICE process. While we acknowledge that the statement has since been superseded in light of the NICE Committee's decision to recommend the Single Target Approach of LDL-C <2.0 mmol/L, we would like to highlight that Section 8.1 (pages 194 to 195) of Developing NICE guidelines: the manual https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869 states that "*A guideline committee cannot usually publish its own recommendations on health technologies covered by published or in development health technologies guidance*" Furthermore, there are several issues with the economic analysis underpinning the modelling of the Treatment Specific Target Approach, including but not limited to the following:	

				• TA733 recommends the use of inclisiran with or **without** other lipid-lowering therapies. The modelling of the Treatment Specific Target Approach used in this guideline only considers inclisiran in combination with ezetimibe and high-intensity statins. • Assumptions around the baseline risk of modifiable CVD mortality • Issues around the utility scores used • Assumptions around treatment adherence Indeed, Page 64, line 19 of the Economic report confirms the Committee's acceptance that there might be uncertainty about the most appropriate unit costs and utilities. In conclusion, the inclusion of the *'Rationale and Impact'* section, while informative for respondents to this consultation, has the potential to confuse and could, therefore lead to divergence of local guidelines & consequent inequities of care. We suggest it should not be included in the final publication, or if necessary,	

				shared as part of a separate document, which has the full context.	
Novartis Pharmaceuticals UK Ltd	Guideline	General	General	The Guideline, as currently written does not appear to weigh heavily towards patient centricity and achieving goal attainment using approved lipid lowering treatments. The economic report and supporting documents, which focus primarily on cost-effectiveness of lipid lowering therapies in Primary care, do not appear to capture the patient's voice. • We recommend including a summary of how the patient voice has been captured in this guideline and/or the supporting document.	Thank you for your comment. Two lay representatives with lived experience were members of the guideline committee. The committee highly valued the experience and opinions of these lay representatives. Their views have been captured as part of the committee's discussion of the evidence in evidence review D. These discussions capture the collective opinion of the committee rather than those of specific committee members.
Novartis Pharmaceuticals UK Ltd	Guideline	General	General	Throughout the guideline there appears to be a lack of consideration of overall cardiovascular risk reduction and the importance of lipid-lowering to achieve this, with comments made such as "*explicitly based on cost-effectiveness*"; "*trade-off between reducing risk and increasing medication should be taken into account*" (page 11, line 7) and "*the committee agreed that recommending ezetimibe to people at lower levels of cholesterol might cause confusion among those who believe their cholesterol to be adequately under control*	Thank you for your comment. These recommendations have been integrated with those on primary prevention in the guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification. This guideline includes further recommendations on the importance of lipid lowering treatments. Recommendation 1.7.10 recommends what to do if the target is not achieved with statin therapy alone and the importance of this is explained in the rationale and committee discussion of the evidence in evidence review D.

				with a statin alone and adherence may be lower for people on 2 pills rather than 1." (page 11, line 8). All these statements seem to imply that treating to target is not the key priority and could leave patients and HCPs, particularly those in primary care who do not have specialist knowledge in lipids, to believe that treating with statin monotherapy is sufficient in all cases. The NHS Long Term Plan sets out an ambition to prevent up to 150,000 cardiovascular events in 10 years, however the inclusion of the following statement "*the committee agreed this increase was necessary for downstream improvements in population health and the extra cost of lipid-lowering treatment would be partly offset by savings due to a reduction in CVD events*" (page 12, line 21) appears to remove the urgency of lipid management, despite elevated LDL-C recognised as a key modifiable risk factor.[1-] Although NICE has focused on cost-effectiveness, it appears that the considerations have not taken into account the true long-term benefits of lipid-lowering on the healthcare system. Follow-up studies of the Scandinavian Simvastatin Survival Study (4S)[2], the West of Scotland Coronary Prevention (WOSCOP) Study[3] and HOPE-3[4] trial have shown continued clinical	The model estimates survival, quality of life and cost benefits over the lifetime based on risk reduction while patients are on treatment. Yes, it does not assume that the reduction in risk of an adverse event continues beyond treatment. This assumption is consistent with other economic models in the area.

				benefits of statins more than 8 years after the trial has been stopped. These initial trials were conducted in the primary prevention population; however, the legacy effect of LDL-C lowering has also been seen in studies involving the PCKS9 monoclonal antibodies in secondary prevention populations[4]. One such study was the ODYSSEY outcomes trial involving the PCSK9 inhibitor alirocumab, which compared alirocumab versus placebo on top of statins, in patients' post-acute coronary syndrome (ACS)[5]. When the study was designed, there were still concerns of reaching very low LDL-C levels during treatment and therefore a conditional stop to the use of alirocumab was imposed in patients who achieved LDL-C levels <0.39mmol/L[5]. A post-hoc analysis showed that not only was there no untoward adverse health effects with very low LDL-C levels but that patients who had LDL-C levels <0.39mmol/L had significantly lower risk of major adverse cardiovascular events over a median follow-up of 2.8 years compared to a matched-placebo controlled group.[6] These studies demonstrate that the reduction of LDL-C levels provides prolonged cardiovascular risk reduction, which extends well beyond trial treatment periods. With this in consideration, cost-effectiveness analyses must take account of the long-term benefits to the health care system in terms of the burden of	

				comorbidities, re-hospitalisations, cardiovascular procedures, disability life-adjusted years, and burden of care to caregivers/social care from these reductions in LDL-C. **References:** 1. Yusuf S, *et al*. *Lancet*. 2004;364(9438):937–952 2. Nayak A, Hayen A, Zhu L, McGeechan K, Glasziou P, Irwig L, et al. Legacy effects of statins on cardiovascular and all-cause mortality: a meta-analysis. BMJ Open 2018;8: e020584. 3. Packard CJ, Ford I. Long-term follow-up of lipid-lowering trials. Curr Opin Lipidol 2015; 26:572–579. 4. Bosch J, Lonn EM, Jung H, Zhu J, Liu L, Lopez-Jaramillo P, et al. Lowering cholesterol, blood pressure, or both to prevent cardiovascular events: results of 8.7 years of follow- up of Heart Outcomes Evaluation Prevention (HOPE)-3 study participants. Eur Heart J 2021;42:2995–3007. 5. Schwartz GG, Gabriel Steg P, Bhatt DL, Bittner VA, Diaz R, Goodman SG, et al. Clinical efficacy and safety of alirocumab after acute coronary syndrome according to achieved level of low-	

				density lipoprotein cholesterol: a propensity score-matched analysis of the ODYSSEY OUTCOMES trial. Circulation 2021;143:1109–1122. 6. Schwartz, GG, et al., Eur Heart J. 2023 Mar 5;44(16):1408-1417	

Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Comments/Action
Novartis Pharmaceuticals UK Ltd	1) Since April 2005, Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain, glycopyrronium bromide: o Seebri® Breezhaler® (glycopyrronium bromide), used as a maintenance	**Status changed from stakeholder to respondent**

	treatment for Chronic Obstructive Pulmonary Disease (COPD) ○ Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide), used as a maintenance treatment for COPD ○ Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate), used as a maintenance treatment for asthma uncontrolled with long-acting beta-agonist (LABA)/inhaled corticosteroid (ICS). Phillip Morris International (a tobacco company) has acquired Vectura Group Limited (formerly Vectura Group plc). Novartis has been granted with an exclusive license from Japan Tobacco Inc. (JT) under JT patents on a world-wide basis for commercial rights to trametinib (Mekinist®; TMT212). Trametinib is a kinase inhibitor indicated as a single agent or in combination with dabrafenib for the treatment of several oncology indications. In 2015, as part of its purchase of oncology products from GlaxoSmithKline, Novartis obtained the worldwide exclusive rights granted by JT	

	to develop, manufacture, and commercialize trametinib. JT retains co-promotion rights in Japan	