NICE National Institute for Health and Care Excellence

Appendix A: Stakeholder consultation comments table

2023 surveillance of CG181 Cardiovascular disease: risk assessment and reduction, including lipid modification (2014)

Consultation dates: 18th November to 1st December 2022

1. Do you agree with the proposal to update cardiovascular disease: risk assessment and reduction, including lipid modification (NICE guideline CG181) to add a 'do not offer' recommendation about aspirin for the primary prevention of cardiovascular disease?

Please give a rationale for your decision.

(Information about when to make a 'do not offer' recommendation can be found in NICE guidelines: the manual section 9.1 Interpreting the evidence to make recommendations).

Stakeholder	Overall response	Comments	NICE response
Diabetes UK	-	We do not hold a strong position on this specific proposal but welcome NICE reviewing the latest evidence, to ensure people living with and at risk of diabetes are accessing the most appropriate treatments.	Thank you for your comments.
NHS Surrey Heartlands ICB	Yes	NHS Surrey Heartlands ICB are keen to support the "do not offer aspirin" recommendation. For most the evidence of benefit is small, and for many the risk of bleeding is as much or more. Accept it is a	Thank you for your comments.

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		cheap drug, but it is also one that, at least in our view, we should not be using routinely for primary prevention.	
HEART UK - The Cholesterol Charity	No	We would suggest it may be too early to make an absolute definitive statement about the value of aspirin in primary prevention and further studies are necessary to support this. However, consideration should be given to distinguishing between the general population and specific high-risk groups There are specific patient cohorts within the primary prevention population who benefit from aspirin therapy, as evidenced by RCT data. One such group is patients with raised Lp(a). The Aspree trial demonstrated that patients with high Lp(a) had improved MACE outcome on aspirin vs placebo, without excess bleeding risk. Aspirin for Primary Prevention of Cardiovascular Events in Relation to Lipoprotein(a) Genotypes | Journal of the American College of Cardiology (jacc.org) Another cohort consists of patients who have undergone coronary artery calcium scoring and found to have CAC score >100. These patients, if at low bleeding risk, derive net benefit from aspirin therapy. https://jamanetwork.com/journals/jamacardiology/fullarticle/2772390	Thank you for your comments. Thank you for highlighting the 2 studies to us. We also identified a small amount of limited evidence suggesting the possibility of net benefit for some subgroups. The first study you have highlighted to us (Lacaze et al. 2022) was not seen during the surveillance review because it postdates the search period (1 March 2017 to 31 August 2022). This study reports a correlation between genotypes associated with elevated levels of lipoprotein(a) (LPA) and major cardiac events (MACE) in people 70 years or older participating in the ASPREE trial, receiving aspirin 100 mg per day. LPA risk was determined using 2 measures: genotyping participants for rs3798220-C, a genotype associated with high LPA in order to establish their carrier status; and by determining participants' LPA-genomic risk score (LPA-GRS). Regression analysis found an interaction between allocation to the aspirin group, MACE and bleeding (p=0.049). It reports increased MACE risk was associated with rs3798220-C carrier status (n=406) in the placebo group (hazard ration (HR): 1.90; 95% CI: 1.11-3.24) but not in the aspirin group (HR: 0.54; 95% CI: 0.17-1.70). Based on these HRs the authors calculated a net benefit of +8.1 per 1000 person years based on 11.4 MACEs avoided versus 3.3 clinically significant bleeds caused. It found no statistically significant interaction between high LPA-genomic risk score and MACE. We acknowledge this may provide limited evidence of net benefit for this genotype but would argue the findings are highly uncertain. The statistical significance in the regression analysis is very borderline and the 95% confidence interval of HR in the aspirin

			group includes harm (i.e., its range includes values greater than 1). It is also noteworthy that genotyping to guide cardiovascular disease prevention is currently very experimental. The second study you have highlighted (Ezimamaka et al. 2020) was not identified by searches because it is not a systematic review or randomised controlled trial. This is a modelling study which aimed to estimate whether coronary artery calcium (CAC) score can be used to identify people who may gain a net benefit from aspirin therapy for primary prevention of MACE. It concludes that individuals with a CAC score of 100 or more, with at least a 5% risk of atherosclerotic cardiovascular disease (ASCVD) who are at low risk of bleeding, may gain a net benefit. It also reports those at high risk of bleeding would experience net harm and reports that higher CAC scores are associated with higher rates of ASCVD and bleeding events. This is a very similar study to one reported in the surveillance report on p.8 (Cainzos-Archirva et al 2020) which suggests a net benefit for people with a CAC score of 100 or more. But like Ezimamaka et al. it uses a modelling method, with its attendant assumptions and uncertainties, making this type of evidence unsuitable on its own for basing recommendations on for this subgroup. Overall, these studies along with those identified during surveillance do not suggest that recommendations can be safely made for offering aspirin to people with high levels of atherosclerotic plaque because they will gain a net benefit. We acknowledge there is emerging research activity around identifying people with high levels of atherosclerotic plaque and

			how this might inform subsequent preventative treatment. Another stakeholder has highlighted to us the ongoing SCOT-HEART 2 Trial. This is investigating whether coronary computed tomography coronary angiography scanning plus risk assessment (ASSIGN cardiovascular risk score) is better than risk assessment alone for guiding treatment to reduce coronary heart disease-related death or non-fatal myocardial infarction in people assessed as being at risk of heart disease. We will track this study and assess its impact on recommendations about primary prevention of CVD when it publishes.
British Geriatrics Society	Yes	Yes we agree d-o not offer aspirin- reading the document and the evidence seems to be the risk of bleed outweighs the risk of cardiovasular mortality.	Thank you for your comments.
British Cardiovascular Society	Yes	Thank you for the opportunity to contribute to this proposal. The British Cardiovascular Society (BCS) would support a change in guidance to include a 'do not offer' recommendation about aspirin for the primary prevention of cardiovascular disease. The BCS found the recent NICE evidence review circulated as part of this consultation to be very thorough and demonstrates a lack of contemporary evidence for the benefit of routine aspirin use in this setting. The BCS considers that there are some areas of uncertainty. For example in people identified from imaging studies as having high atherosclerotic plaque burden or features of vulnerable plaque and significant unmodifiable CV risk factors. The ongoing SCOT-HEART2 study may provide further evidence here.	Thank you for comments and for highlighting to us the ongoing SCOT-HEART 2 Trial. This is investigating whether coronary computed tomography coronary angiography scanning plus risk assessment (ASSIGN cardiovascular risk score) is better than risk assessment alone for guiding treatment to reduce coronary heart disease-related death or non-fatal myocardial infarction in people at risk of heart disease. This is a large study that could produce good evidence for or against a net benefit for aspirin for people with high levels of atherosclerotic plaque. We will track it and assess its impact on recommendations relating to primary prevention of CVD when it publishes. Thank you for the suggested alternative wording and highlighting areas of uncertainty. We would like to be able to make a nuanced recommendation of the type you suggest, but we have not seen any evidence yet that will allow us to do so safely. On balance evidence

		The BCS would like to suggest some potential wording for a recommendation: *'Do not offer aspirin for primary prevention in patients with asymptomatic atherosclerotic disease unless recommended by a specialist after careful consideration of the risks of cardiovascular events and bleeding'.*	suggests benefit is off set (and for some studies outweighed) by risk in people without manifest CVD and that overall, a 'do not offer' recommendation is warranted. Additionally, the ASCEND trial suggests aspirin-induced bleeding may increase with cardiovascular risk, potentially confounding the identification of those at high risk of MACE but low risk of bleeds. We did identify a small volume of evidence for a possible net benefit for people with high levels of atherosclerotic plaque, but it is limited in quality. Further good quality data is needed, before recommendations about this subgroup can be considered for development.
Astra Zeneca	NA	Thank you for the opportunity to review the consultation on CG181 to date. At this stage AstraZeneca do not have any comments to add. We look forward to seeing this update progress and our involvement in the next step.	Thank you for your comments.
Learning Disability and Autism Programme, NHS England		Our programme would like to highlight that: • There is a need for additional clinical assessment to be undertaken and consideration to be given regarding additional syndromes and their potential impact when 'do not offer' is being included as an option for people with a learning disability. Simply having a learning disability should not be a reason for not offering.	Thank you for your comments and the important points you have raised. We have addressed each comment below. • 'There is a need for additional clinical assessment…Simply having a learning disability should not be a reason for not offering'. Currently CG181 makes several recommendations about involving patients in discussion about CVD risk and treatment (CG181-1.1.22-28). During guideline development people with learning disabilities

		• The ASPREE trial excluded people with a disability from the population studied. • The 'do not offer' aspirin would be appropriate given the new evidence base. • There is no mention in the guideline at all about health inequalities. From the perspective of the national autism and learning disability programme, this is of great concern. We would like NICE to take the opportunity to strengthen the guidance to ensure that access to screening and advice is improved, through reasonable adjustments and proactive taking of opportunities "every contact counts." The very concepts within the guideline are quite technical and complicated, even when simplified to discussions about 'good' and 'bad' cholesterol. For our learning disability population, this is especially difficult. Asking some of this group to keep their dietary total and saturated fat intake below a certain % of daily intake is quite complex. Evidence for our statement: We know from LeDeR (2021) that on average, men with a learning disability die 22 years younger than men from the general population, and women 26 years younger than women the general population. People with a learning disability from ethnic minority backgrounds, and those living in deprived areas, have even poorer outcomes. Cardiovascular disease was the leading cause of death in 14.3% cases reported in the 2021 LeDeR report. Recent serious incident and national and local reviews of inadequate hospital care	were considered as part of the equality impact assessment and the recommendations page highlights that people have the right to make informed decisions about their care. It includes a link to 'Making decisions using NICE guidelines' which links to information about professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding. The proposal to add a 'do not offer' recommendation is based on clinical evidence of a high probability that there is no benefit and possibly a risk associated with aspirin for primary prevention of CVD. We did not identify clinical evidence to suggest that this negative benefit-risk balance does not apply to people with learning disabilities, although I note your comment about the ASPREE trial which I have addressed below. The recommendation is proposed on this basis, and it should be applied by healthcare professionals to all NHS service users based on this consideration alone. In the 'your responsibility' section on the overview page of CG181 it states: 'When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service.' • 'The ASPREE trial excluded people with a disability from the population studied.' The ASPREE study protocol does not exclude all people with a disability and it is not listed as an exclusion criteria. We note however that it does exclude people who have severe difficulty or an inability to perform any one of the 6 activities of daily living (ADL) measured by the Katz ADL index. This is because it is trying to measure whether aspirin reduces the rate of cardiac induced disabilities in an older population. It should be noted that the other

		e.g. https://www.norfolksafeguardingadultsboard.info/assets/SARs/SAR-Joanna-Jon-and-Ben/SAR-Rpt-Joanna-JonBen_FINAL-PUBLICATION02-June2021.pdf highlight the difficulty people with a learning disability and autistic people have in accessing primary health care when in a mental health hospital, yet they have very high risks owing to forced inactivity in hospital, high use of antipsychotic medication and unhealthy diet, (all leading to obesity), with the additional disadvantage of poor access to primary care from within hospital.	large trials that triggered this review, ASCEND and ARRIVE , do not exclude people with disabilities. • There is no mention in the guideline at all about health inequalities. The impact of recommendations on people with protected characteristics was assessed as part of the equality impact assessment. Thank you for providing evidence about the reduced life expectancy of people with learning disabilities. Challenging behaviour and learning disabilities (NICE guideline NG11) section 1.2 recommends an annual physical health check including a review of all current health interventions, including medication and related side effects, adverse events, drug interactions and adherence. This guideline also makes recommendations about how to work with people with learning disabilities in its general principles of care section 1.1. Additionally autism spectrum disorder in adults (NICE guideline CG142) recommendation 1.1.9 recommends that '*all health and social care professionals providing care and support for autistic adults should be aware of under-reporting and under-recognition of physical disorders in autistic people.*' We acknowledge your comments about the technical and complex nature of some of the recommendations in CG181. However, it should be noted that NICE's guidelines are aimed at healthcare professionals and not lay persons, although they do contain recommendations about good practice in shared decision making. NICE is unable to comment on specific safeguarding and care incidents but NG11-1.1.4 recommends that *'health and social care provider organisations should ensure that teams carrying out assessments and delivering interventions recommended in this guideline*

			have the training and supervision needed to ensure that they have the necessary skills and competencies.'
Royal College of Physicians	Yes	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the British Cardiovascular Society (BCS)	Thank you for your response.

2. "Are you aware of any issues related to inequalities for specific subgroups of the population?

Please provide details on any issues."

Stakeholder	Overall response	Comments	NICE response
Diabetes UK	NA	*No answer given*	
NHS Surrey Heartlands ICB	No	NHS Surrey Heartlands ICB cannot think of any inequality related issues with aspirin.	Thank you for your response.
HEART UK - The Cholesterol Charity	No	None	Thank you for your response.

British Geriatrics Society	No	We are not aware of inequalities so have nothing to add to the second statement	Thank you for your response.
British Cardiovascular Society	No	We are not aware of any specific issues related to inequalities for specific subgroups of the population.	Thank you for your response.
Astra Zeneca	NA	Thank you for the opportunity to review the consultation on CG181 to date. At this stage AstraZeneca do not have any comments to add. We look forward to seeing this update progress and our involvement in the next step.	Thank you for your response.
Learning Disability and Autism Programme, NHS England	NA	*No answer given*	
Royal College of Physicians	No	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the British Cardiovascular Society (BCS)	Thank you for your response.

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