NICE National Institute for Health and Care Excellence

2023 exceptional surveillance of cardiovascular disease: risk assessment and reduction, including lipid modification (NICE guideline CG181)

Surveillance report

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Surveillance decision

After consulting with stakeholders, we will update the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification to add a do not routinely offer recommendation about the use of aspirin for the primary prevention of cardiovascular disease (CVD).

Stakeholders highlighted to us the ongoing SCOT-HEART 2 trial, which is investigating computed tomography coronary angiography's role in guiding preventative treatment of CVD. We will assess the impact on recommendations about aspirin in the NICE guideline, when it publishes data in 2027.

Trigger for this exceptional surveillance review

Members of NICE's CVD committee highlighted to us new evidence about aspirin for the primary prevention of CVD from the ASCEND, ASPREE, and ARRIVE studies. These are large trials investigating the efficacy of aspirin in various populations considered to be at risk of CVD.

Rationale for the surveillance decision

ASCEND, ARRIVE and ASPREE report that while the use of aspirin for primary prevention of CVD does reduce the rate of cardiovascular events, the benefit is largely offset by the risks from increased rates of bleeding. This finding is reported consistently by other studies we identified during this surveillance review. While some studies suggest an increased benefit for specific cardiovascular events, for example, stroke and myocardial infarction (MI), compared with composite cardiovascular outcomes, and for specific subgroups, for example, those at low long-term risk, non-smokers or those taking statins, this increased benefit is unlikely to outweigh the risks posed by bleeding. We identified limited evidence for net benefit in some subgroups, but it is largely from modelling studies, which are not enough to base recommendations on because of their level of uncertainty.

Stakeholders highlighted to us that people with increased levels of atherosclerotic plaque may benefit from aspirin for primary prevention and provided evidence in support of this. Evidence for this group was also identified by surveillance searches and it is assessed as currently being too limited in quality and volume to base recommendations on. However,

stakeholders also highlighted the ongoing SCOT-HEART 2 trial, which may yield evidence for the role of computed tomography coronary angiography, a method for measuring plaque levels, in guiding preventative treatment. We will track this and assess its impact when it publishes data.

For further details and a summary of key evidence identified in surveillance, see the summary of evidence from surveillance.

Overview of 2023 surveillance methods

NICE's surveillance team checked whether recommendations in NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification, remain up to date:

- Considering conclusions from the ARRIVE, ASCEND and ASPREE trials highlighted to us by NICE's CVD expert committee.
- Examining related NICE guidance and quality standards.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify additional relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting with members of NICE's GP reference panel about the prescribing of aspirin in primary care.
- Consulting with a NICE consultant clinical adviser.
- Consulting on the proposal with stakeholders.

For further details about the process and the possible update proposals that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in surveillance

ARRIVE, ASCEND and ASPREE trials

The ARRIVE trial (Gaziano et al. 2018) investigates cardiovascular events in adults (n=12,546) aged 55 years or older without type 2 diabetes, with no history of vascular events, (MI, stroke, coronary artery angioplasty, stenting, coronary artery bypass graft, arrhythmias, congestive heart failure or vascular intervention), who were randomised to receive aspirin (100 mg daily) or placebo. It reports no difference at 60 months in incidence of a first cardiovascular event (a composite of cardiovascular death, MI, unstable angina, stroke, or transient ischaemic attack [TIA]; hazard ratio [HR]=0.96; 95% confidence interval [CI] 0.81 to 1.13; p=0·6038) but a higher risk of gastrointestinal (GI) bleeding in the aspirin group (HR 2.11; 95% CI 1.36 to 3.28; p=0·0007). The GI bleeding events were assessed as mostly mild, and the number of serious adverse events was similar in both groups: n=1,266 (20.19%) aspirin group versus n=1,311 (20.89%) placebo group. The number of documented deaths (n=321) were also similar: n=160 (2.55%) occurred in the aspirin group and n=161 (2.57%) in the placebo group. The authors note that the cardiovascular event rate was lower than anticipated (less than 5% in both groups) and they considered the study sample more representative of a low risk population.

The ASCEND trial (The ASCEND Study Collaborative Group 2018) investigated cardiovascular events in adults (n=15,480) with type 1 or type 2 diabetes without CVD, aged 40 years or older, receiving aspirin (100 mg daily) or placebo. It reports that at 7.4 years follow-up there was a reduced incidence of serious cardiovascular events (a composite of MI, stroke or TIA, or death from any vascular cause, excluding any confirmed intracranial haemorrhage) in the aspirin group (risk ratio [RR]=0.88; 95% CI, 0.79 to 0.97; p=0.01). A higher rate of bleeding events (GI and extracranial bleeding) was observed in the aspirin group (RR=1.29; 95% CI, 1.09 to 1.52; p=0.003). There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (2.0% in each group) or all cancers (11.6% aspirin and 11.5% placebo). The study reports a number needed to treat of 91 to avoid a serious vascular event and a number needed to harm of 112, for example, a small positive benefit-risk balance. ASCEND reports that when participants were stratified by baseline estimated 5 year risk of a serious cardiovascular event, the risk of bleeding also increased. This was reported as follows for the aspirin group:

ASCEND trial results from participants stratified by baseline estimated 5 year risk of a serious cardiovascular event

Estimated 5 year risk of a cardiovascular event	Serious vascular events or revascularizations avoided per 5,000 person years	Major bleeding caused per 5,000 person years
Less than 5%	6.1	2.8
5% to less than 10%	13.4	8.9
10% risk or higher	11.3	9.6

This data would suggest cardiovascular risk and aspirin-induced bleeding are covariables with net benefit remaining positive but reducing with increasing 5 year risk.

The ASPREE trial (ASPREE Investigator Group 2018) investigated cardiovascular events in adults (n=19,114) without CVD, dementia or disability with a median age of 74 years based in Australia and the US, who were receiving aspirin (100 mg daily) or placebo. The study's primary endpoint was a composite of death, dementia, or persistent physical disability. At 4.7 years follow-up it reports no significant difference between groups (HR, 1.01; 95% CI, 0.92 to 1.11; p=0.79). It also reports a higher level of major bleeding in the aspirin group that was statistically significant compared with placebo (3.8% versus 2.8%; HR, 1.38; 95% CI, 1.18 to 1.62; p<0.001).

The trial also reports a higher risk of death from any cause in the aspirin group compared with the placebo group (HR, 1.14; 95% CI, 1.01 to 1.29), with cancer the major contributor (HR, 1.31; 95% CI, 1.10 to 1.56; 1.6 excess deaths per 1,000 person years in the aspirin group). With respect to cardiovascular outcomes, the trial reports no difference between groups for CVD events (a composite of fatal coronary heart disease, nonfatal MI, fatal or nonfatal stroke or hospitalisation for heart failure; HR, 0.95; 95% CI, 0.83 to 1.08). The authors conclude that there is no benefit from aspirin for disability-free survival or for preventing CVD but that there is an increased risk of major bleeds. The authors urge caution over interpretation of the result associating excess cancer deaths with aspirin. They note it runs counter to studies showing a protective effect and that a plausible mechanism for harm is unclear.

Overall conclusions from ASCEND, ASPREE and ARRIVE

These studies strongly suggest that at best the benefit-harm balance for aspirin is very

close and for some groups harms outweigh benefits. These findings are consistent with current recommendations in the NICE guidelines on type 1 diabetes in adults: diagnosis and management and type 2 diabetes in adults: management, which both recommend that clinicians do not offer antiplatelets including aspirin to adults with diabetes without CVD. However, the conclusions suggest a similar recommendation may need to be added to NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification.

Additional evidence

We searched for additional evidence related to the use of aspirin for primary prevention of CVD. We found 66 published studies in a search for randomised controlled trials and systematic reviews published between 1 March 2017 and 31 August 2022. The search also identified the ongoing ATTACK trial (aspirin to prevent a first heart attack or stroke in people with chronic kidney disease). This was assessed as having the potential to change recommendations therefore we plan to evaluate the impact of the results on current recommendations when it publishes

Including ATTACK, we considered 67 studies to be relevant to the guideline. Additional evidence is not summarised in its entirety in this document as most of it concurred with the conclusions of ASPREE, ASCEND and ARRIVE; that overall, the increased rate of bleeds from aspirin outweighs or is very similar to the reduced rate of cardiovascular events. Additional evidence included 3 notable meta-analyses with data from one or more of ASPREE, ASCEND and ARRIVE. These are summarised below.

Meta-analyses that include one or more of ASPREE, ASCEND and ARRIVE

A meta-analysis (Zheng et al. 2019) of 13 trials including ARRIVE, ASCEND, ASPREE (n=164,225 participants, 19% with diabetes) reports aspirin reduces cardiovascular events (a composite of cardiovascular death, nonfatal MI, and nonfatal stroke) with an absolute risk reduction (ARR) of 0.38% (HR, 0.89, 95% CI, 0.84 to 0.95) compared with no aspirin. It reports aspirin was not associated with a reduction in all-cause or cardiovascular mortality. The study also reports that the incidence of serious bleeds is increased (HR, 1.43, 95% CI, 1.30 to 1.56) with an absolute risk increase (ARI) of 0.47% when aspirin was compared with no aspirin. The study estimates a number needed to treat (NNT) of 265 for avoiding 1 composite cardiovascular event, and the number needed to harm (NNH) of 210 for major bleeds, for example, an overall net negative benefit-risk balance. NNH increases

to 927 for intercranial bleeds and 334 for major GI bleeds. NNT for MI and ischaemic stroke are reported as 361 and 540, respectively. In studies in which participants were considered to be at low risk of a cardiovascular outcome, aspirin was associated with reductions in the composite cardiovascular outcome (HR, 0.91, 95% CI, 0.84 to 0.98); an ARR of 0.63% (95% CI, 0.18% to 1.03%); equivalent to a NNT of 160. It was not associated with a reduction in all-cause mortality, cardiovascular-related mortality, MI, and stroke. This corresponded with an increased risk of major bleeding (HR, 1.45, 95% CI, 1.28 to 1.63) an ARI of 0.40% (95% CI, 0.25% to 0.57%) equivalent to an NNH of 249. This would suggest a net benefit, however this result is not explored and may be due to covariables. It was further reported that for participants with diabetes (n=30,448) aspirin was associated with a reduction in cardiovascular events (HR, 0.90, 95% CI, 0.82 to 1.00), an ARR of 0.65% (95% CI, 0.09% to 1.17%) equivalent to an NNT of 153. However, aspirin use was associated with an increase in major bleeding in this group which offset any benefit (HR, 1.29, 95% CI, 1.11 to 1.51), an ARI of 0.80% (95% CI, 0.29 to 1.39%) equivalent to an NNH of 121.

Another meta-analysis (Gelbenegger et al. [2019]; n=162,255) investigated net clinical benefit of aspirin on all-cause mortality. The outcome was weighted for type of major cardiac event (MACE) and bleeds according to an event's relative impact on mortality. This weighting was derived from the literature about the death-related risk of MI, ischaemic stroke, haemorrhagic stroke, and major extracranial bleeding. It reports overall no net clinical benefit for aspirin (0.034%; 95% CI, -0.184 to 0.252%). NNT and NNH for MACE was calculated per 10,000 patients per year. It reports an ARR of 0.052% for MACE, equivalent to an NNT of 1,908; an MI ARR of 0.041%, an NNT of 2,452; and a stroke ARR of 0.022%; NNT 4,448. However, it reports aspirin is associated with major bleeding with an ARI of 0.077%, equivalent to an NNH of 1,295. This is a relative risk reduction (RRR) for MACE of 9% (n=164,225) compared with a relative risk increase of major bleeds of 46% (n=159,086), for example, overall a negative net benefit-risk balance.

The study also carried out several subgroup analyses. It reports:

- Aspirin-treated patients who were also treated with statins (n= 34,594, from ASCEND and ASPREE) had an increased RRR of 12% for MACE when compared with control plus statin. People treated with aspirin only did not reduce MACE risk when compared with a control.
- Smokers versus non-smokers: 5 trials (including ASPREE and ARRIVE; n=88,539) reported in non-smokers, aspirin use was associated with a 10% RRR of MACE compared with no aspirin. In smokers, aspirin did not affect the risk of MACE.

- Gender: 9 trials (including ASCEND and ASPREE; n=59,337), MACE risk reduction was statistically significant in men but not women. This greater reduction did not hold for MI and was reversed for stroke where there is an effect in women but not men (4 randomised controlled trials [RCTs] n=71,271).
- Diabetes: 6 RCTS (including ASCEND and ASPREE) reported no difference in RRR of MACE between all participants and those with diabetes (9%). However, 4 RCTs (including ASCEND) showed a greater reduction of ischaemic stroke, (n=20,332; RRR of 24%).

A third meta-analysis (Abdelaziz et al. 2019; n=165,502), 15 trials including ARRIVE, ASCEND and ASPREE of which 11 included participants considered to have a high 10 year risk of CVD, also reports aspirin is not superior to placebo for all-cause mortality, cardiovascular- and non-cardiovascular-related mortality (respectively: RR: 0.97, 95% CI: 0.93 to 1.01; RR: 0.93, 95% CI: 0.86 to 1.00; and RR: 0.98, 95% CI: 0.92 to 1.05). Aspirin was associated with lower risk of total MI (2.07% versus 2.35%; RR: 0.85; 95% CI: 0.76 to 0.95; p=0.003), compared with control groups. The risk of fatal MI, angina pectoris and coronary revascularisation were similar between aspirin and controls. Aspirin was associated with a higher risk of major bleeding, intracranial bleeding, and major GI bleeding (respectively: RR: 1.5, 95% CI: 1.33 to 1.69; RR: 1.32, 95% CI: 1.12 to 1.55 and RR: 1.52, 95% CI: 1.34 to 1.73). Risk of TIA was lower in the aspirin group (1.06% versus 1.33%; RR: 0.79; 95% CI: 0.71 to 0.89; p<0.001). Total stroke rates were similar in the 2 groups. Subgroup analysis revealed a lower risk of ischaemic stroke (1.29% versus 1.49%; RR: 0.87; 95% CI: 0.79 to 0.95; p=0.002; I^2=0%), but a trend toward a higher risk of haemorrhagic stroke (0.29% versus 0.23%; RR: 1.21; 95% CI: 0.99 to 1.47; p=0.059). The NNTs for MI, TIA, and ischaemic stroke were 357, 370, and 500, respectively. Like the other meta-analyses described above, the study reports aspirin is associated with an increase in major bleeding (1.47% versus 1.02%; RR: 1.50; 95% CI: 1.33 to 1.69; p<0.001). Specifically, there is an association with intracranial bleeding including haemorrhagic stroke (0.42% versus 0.32%; RR: 1.32; 95% CI: 1.12 to 1.55; p=0.001), and major GI bleeding (0.80% versus 0.54%; RR: 1.52; 95% CI: 1.34 to 1.73; p<0.001) compared with control groups. Fatal bleeding was similar between aspirin and controls (0.23% versus 0.19%; RR: 1.09; 95% CI: 0.78 to 1.55; p=0.6). The NNHs for a major bleeding event and intracranial bleeding were 222 and 1,000 respectively. The former figure is lower than NNTs for MI, TIA and ischaemic stroke suggesting a net negative benefit-risk balance.

Studies suggesting a role for aspirin in primary prevention

A modelling study (Cainzos-Achirica et al. 2020) investigated the effectiveness of

coronary artery calcium (CAC) for identifying people at higher risk of atherosclerotic CVD (ASCVD) risk but not at high risk of bleeding. Aspirin is recommended for primary prevention of CVD in the American College of Cardiology (ACC) / American Heart Association (AHA) primary prevention guidelines (see non-NICE guidelines about aspirin) for people 40 to 70 years old with low risk of bleeding.

The study estimated the ability of CAC to identify those who would most benefit from aspirin for primary prevention by using a subset of participants from the MESA (Multi-Ethnic Study of Atherosclerosis) study (n=3,540) who were: aspirin-naïve, less than 70 years old, and assessed as being at low risk of bleeding. The study modelled the benefit-risk of aspirin for people in specific at risk categories using data about MESA participants' ASCVD risk (<5% risk; 5 to 20%; and >20%) and CAC scores (CAC=0, CAC 1 to 99, and CAC>=100, CAC>=400), and using an RRR at 5 years for CVD of 12% and a relative risk increase (RRI) at 5 years for major bleeds of 42% from a recent meta-analysis (Zheng. et al 2019). The NNT and NNH were then estimated for hypothetical cardiovascular events avoided and bleeds caused. The estimates suggest with a CAC score 100 or greater, the NNT (140) would be lower than the NNH (518) suggesting an overall net benefit for people with a high level of atherosclerotic plaque. For ASCVD 5 year risk strata the NNT was nearly double the NNH for low risk (1,543 vs 794) participants and was similar for medium (292 versus 229) and high risk (251 versus 256) participants. The authors conclude that tomographic CT screening for CAC may improve identification of people likely to gain a net benefit from aspirin. The study has some limitations: firstly, the authors note there are differences between the population from which the cardiovascular and bleed prevalence estimates are derived and the MESA population. This limits the RRR and RRI transferability from one population to the other and the authors note NNH and NNT estimates are sensitive to these differences. Secondly, the MESA data lacked some information about bleeding risk such as history of gastrointestinal ulcers. The authors also acknowledge the heterogeneity of the studies underpinning the prevalence estimates used in the model.

A decision analysis (Dehmer. et al 2022) undertaken for the US Preventive Services Task Force was identified. This decision analysis investigated CVD and colorectal cancer outcomes in people taking aspirin (100 mg or less daily). It reports that when benefits are expressed as quality adjusted life years (QALYs), the lifetime net benefits from low dose aspirin for primary prevention were positive for adults with >=5% 10-year CVD risk if they started taking it between the ages 40 to 59 years. Those with a >=10% 10-year CVD risk only gained a net benefit if they started taking aspirin between the ages of 60 to 69 years. Lifetime gains in QALYs ranged from 2.3 to 66.2 per 1,000 persons. The analysis assumes

that aspirin harms in the first 10 years of use exceed the benefits. This study updates an analysis from 2016 and the authors note that it demonstrated much smaller margins for net benefit than its predecessor. Current ACC/AHA recommendations are partly based on this analysis.

A systematic review (Lin et al. 2018; n=43 studies) was identified that was also carried out to inform the US Preventive Services Task Force guidelines about primary prevention of CVD. The study aimed to answer 5 questions about the clinical impact of non-traditional risk factor assessment versus traditional risk factor assessment using the Framingham Risk Score (FRS) or Pooled Cohort Equations. The study concludes there is only indirect evidence mostly limited to studies evaluating the incremental value on discrimination and risk reclassification when adding ankle-brachial index (ABI), high sensitivity c-reactive protein (hsCRP), or CAC to the FRS. It notes that ABI may improve discrimination and reclassification in women, and CAC moderately improves identification but the effect on downstream healthcare use is uncertain. It notes a single large RCT reports high-intensity statin therapy in individuals with elevated hsCRP and normal lipid levels can reduce CVD morbidity and mortality.

Intelligence gathered during surveillance

Views from NICE's GP reference panel

We considered the views of members of NICE's GP reference panel. We asked them if there was controversy among primary care practitioners about whether or not to prescribe aspirin for the primary prevention of CVD.

Two commented that there was no great controversy about whether or not to prescribe aspirin for primary prevention. One GP commented that after an era where aspirin in primary prevention was widespread, GPs have firmly received a different message over the last 20 years that there is not a favourable benefit-harm ratio in primary prevention and therefore that it should not be prescribed for primary prevention.

They also noted that some trials in the last few years may suggest a benefit for higher risk primary prevention patients; that this would require some extrapolation and that it might be worth exploring. They concluded by commenting that if NICE is not going to make a do not offer recommendation then it would be helpful to produce a decision aid about the relative benefits and harms to enable a shared decision. One GP commented that any such

aid would benefit from risk-benefit statistics such as NNT and NNH that might be more meaningful to patients than probabilities.

It was noted by one of the respondents that the issue of aspirin for primary prevention had been slightly complicated by that of aspirin's benefits for people with low GI calcium. No evidence about this issue was identified during this surveillance.

One GP provided a short narrative review that assesses the impact of the latest evidence and current guidelines on prescribing of aspirin for primary prevention. The paper suggests 4 issues for consideration for clinicians considering prescribing aspirin for primary prevention.

Non-NICE guidelines about aspirin

We were alerted to the International Aspirin Foundation, which maintains a library of guidelines about aspirin produced by UK, European, and US centres.

UK guidelines

Risk estimation and the prevention of cardiovascular disease (SIGN guideline 149). Recommendation 2.5 states that aspirin is not recommended for primary prevention of CVD.

European guidelines

The European Society of Cardiology (ESC) features (key message 3a.10), which states that antiplatelet therapy is not recommended in individuals free from CVD, due to the increased risk of major bleeding.

They also recommend:

- Patients with diabetes mellitus and symptomatic CVD should be treated no differently to patients without diabetes mellitus (DM).
- In patients with DM at moderate CV risk, aspirin for primary prevention is not recommended.
- In patients with DM at high/very high risk, aspirin may be considered in primary prevention.

The ESC does not recommend aspirin for people aged over 70 years following the results of ASPREE and that benefits for primary prevention remain unclear following ARRIVE.

The ESC note that following ASCEND, the benefit-risk ratio for people with diabetes using aspirin for primary prevention is balanced and low dose aspirin is not protective against cancer (see ESC press release following ASCEND).

US guidelines

ACC/AHA guidelines on the primary prevention of CVD features (4.6 aspirin use), which recommend considering low dose aspirin therapy (75 to 100 mg orally daily) only among adults 40 to 70 years of age who are at higher ASCVD risk but not at high risk of bleeding.

Conclusions and impact assessment

The published empirical evidence seen during this surveillance review strongly suggests that the benefit from aspirin for primary prevention for reducing the risk of cardiovascular events is very closely balanced or outweighed by the increased risk of bleeds. Although there seems to be greater benefit than the aggregate of cardiovascular events for some subgroups for specific cardiovascular events, generally those increases do not trade off the balance between harm and benefit. There is a small amount of evidence from one study (Zheng et al. 2019) seen during this surveillance that people without manifest CVD estimated to be at a low risk of CVD outcomes may gain a net benefit from aspirin. However, this conclusion is from a pooled analysis subject to covariate effects and the interactions between these covariates are not discussed. Results from the ASCEND trial suggest a potentially small net benefit in those with diabetes at low long-term risk of CVD while also suggesting that bleed risk increases with increased cardiovascular risk. This suggests that identifying people with low risk of bleeds who also stand to gain large benefits from aspirin because they are at elevated long-term risk of CVD, may be difficult.

Limited evidence was identified during this surveillance about new methods in addition to standard techniques for identifying those who may gain a net benefit from aspirin. A modelling study investigating the utility of CAC scores suggests people with scores of 100 or more may gain a net benefit from aspirin. However, this is not empirical evidence, and it makes several assumptions about cardiovascular event and bleed prevalence that may have impacted the result.

Additionally, a health economic study was identified that estimates a lifetime gain in QALYs

for aspirin for primary prevention when CVD and colorectal cancer outcomes are considered, and when administration is conditional on age and CVD risk. This updated review notes that for most groups aspirin's harms are likely to outweigh benefit in the first 10 years of use, and that for those likely to receive a net benefit that the margin is likely to be small.

There is evidence from the COMPASS trial that proton pump inhibitors (PPIs) have a protective effect on gastrointestinal bleeding. The COMPASS trial was conducted with participants with stable CVD and concludes that pantoprazole significantly reduces bleeding from gastroduodenal lesions but not GI events. As noted by Gelbenegger et al. (2019); summarised above, it is uncertain how desirable it is for patients without bleeding risk to be given PPIs concurrent with aspirin for primary prevention. Long-term use of PPIs is associated with various adverse effects including hypomagnesemia, a known cause of cardiac arrhythmias.

The NICE clinical knowledge summary (CKS) on antiplatelet treatment for primary prevention of CVD cautiously recommends aspirin for primary prevention for people at high risk of stroke and MI. It cautions that if aspirin is being considered, to discuss the risks and benefits with the individual. While it should be noted that the CKS is not a formal guideline, we will update it to bring it in line with the update of the NICE guideline. Patient choice is an important consideration for the NICE guideline (recommendations 1.1.22 to 1.1.28) and it may be that a person may accept the risk of a mild bleed in preference to a potentially very serious outcome associated with a cardiovascular event. However, as Gelbenegger et al (2019) also noted, it is difficult to attach a score to one adverse outcome in order to assess it against another in a way that is meaningful. Additionally recommendation 1.1.7 states to be aware that all CVD risk assessment tools can provide only an approximate value for CVD risk. Interpretation of CVD risk scores should always reflect informed clinical judgement.

Two GPs consulted during this surveillance commented that the risks from aspirin when used in people without CVD are well known to GPs and that there is no great controversy about not prescribing it for primary prevention. New evidence identified during this surveillance supports the fact that there is at best a very close benefit-risk balance and when aggerated across subgroups and outcomes largely a negative benefit-risk balance. After considering all the latest evidence and intelligence it is concluded the risks are likely to outweigh the benefits and that the NICE guideline should be amended to make a do not routinely offer recommendation for the use of aspirin for primary prevention of CVD.

Views of stakeholders

We received responses from 8 stakeholders comprising: 3 charity organisations, 1 NHS integrated care board, 1 professional society, 1 royal college, 1 pharmaceutical manufacturer, and NHS England's learning disability and autism programme. Five agreed with adding a do not offer recommendation, 1 disagreed and 2 did not give a yes or no response. The stakeholder who disagreed suggested that there may be a benefit for people genetically predisposed to have high levels of lipoprotein-a (LPA) from the ASPREE trial. They highlighted evidence that suggests a high risk for people with a specific genotype whose risk of MACE was attenuated by aspirin. However, the study reports very borderline statistical significance with very high uncertainty and confidence intervals that encompass no benefit. This evidence currently is too uncertain and insufficient to be used to base recommendations on for this group. They also provided evidence that people with high CAC scores may benefit from aspirin. This evidence was very similar to the modelling study about CAC scores identified in this surveillance review and is not sufficient to base recommendations on. The same subgroup was also highlighted by a second stakeholder as having the potential to gain a net benefit from aspirin for primary prevention. They also highlighted to us the ongoing SCOT-HEART 2 trial. This is designed to generate robust evidence for the role of computed tomography coronary angiography in guiding preventative treatment, including the use of antiplatelets. We will track this study and assess its impact on recommendations when it publishes in 2027. Overall evidence, including that provided by stakeholders, is assessed as currently insufficient to safely make recommendations about the use of aspirin for primary prevention of CVD with people with higher levels of atherosclerotic plaque.

One stakeholder commented on the risks of making a do not offer recommendation and people with learning disabilities, and for improving the NICE guideline with respect to this group. This is discussed in the equalities section.

See appendix A for full stakeholder comments and responses.

Previous surveillance

Surveillance was carried out in 2018. No new evidence about aspirin for the primary prevention of CVD was identified.

Equalities

The equality impact assessment for the NICE guideline acknowledges that the following subgroups require specific attention in relation to making recommendations about CVD risk assessment and reduction: black and minority ethnic groups; people with a family history of CVD; low socio-economic groups; people aged over 75 years; women; people with auto-immune disease; and people with mental illness. A stakeholder commented that if a do not offer recommendation is added to the NICE guideline about aspirin for primary prevention it would benefit from additional clinical assessment recommendations that account for different syndromes associated with learning disabilities and autism. They also commented that the presence of a learning disability on its own should not be a reason for not offering an intervention.

During this surveillance review we did not identify evidence suggesting the risk-benefit ratio for aspirin for primary prevention differs in people with learning disabilities or autistic people compared to the general population. Any do not offer recommendation should therefore be applied to this group based on their clinical presentation and in line with the your responsibility information given on the overview of the NICE guideline. This 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 stakeholder also highlighted that people with learning disabilities, on average, have shorter lifespans than the general population and that cardiovascular death was a leading cause of mortality. This issue is addressed by section 1.2 in NICE's guideline on challenging behaviour and learning disabilities, which 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. The same guideline also makes recommendations about how to work with people with learning disabilities, see section 1 in NICE's guideline on challenging behaviour and learning disabilities.

Overall decision

After considering all evidence and other intelligence and the impact on current recommendations, it is decided that a do not routinely offer recommendation about the use aspirin for primary prevention of CVD should be added to NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification.

We will track the SCOT-HEART 2 trial and reassess recommendations about aspirin for primary prevention when it publishes data in 2027.

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