NICE National Institute for Health and Care Excellence

HealthTech Programme

Drug-eluting stents for treating coronary artery disease: Late-stage assessment

Draft guidance comments

Theme 1. Having access to a range of stents

Comment no.	Consultee	Section no.	Comment	NICE response
1.	Consultee 1	Not specified	The [consultee 1] supports the recommendations made.	Thank you for this comment.
2.	Consultee 3	1.1 1 Recommendations	We fully support NHS trusts having access to a range of DES for both clinical and supply reasons. Lesions and patients can vary in many ways, and no single DES can be used in all lesion and patient types.	Thank you for this comment.
3.	Consultee 4	1.1 1 Recommendations	We agree with this recommendation and appreciate that it is built on clinical appropriateness.	Thank you for this comment.
4.	Consultee 6	Recommendation 1.1	We agree that NHS trusts should provide access to a range of drug-eluting stents, so that a clinically appropriate stent is available for everyone with coronary artery disease.	Thank you for this comment.

Theme 2. Rationale for 'no justification for price variation'

Comment no.	Consultee	Section no.	Comment	NICE response
5.	Consultee 2 Interventional Systems	1.2 1 Recommendations	The conclusion that the assessed stents are comparable in terms of clinical and cost effectiveness is misleading, not only for the clinical professionals decision making, but also for the patients' safety and for	Thank you for this comment.

Comment no.	Consultee	Section no.	Comment	NICE response
			the Commissioners when choosing the best value for money technology for the NHS ressources. In fact this LSA covers 29 drug eluting stents currently available through NHS Supply Chain. For 8 of the 29 stents there was no randomised and comparative evidence, and only 18 of the 29 stents had sufficient evidence to be included in the network metanalysis (NMA). The LSA considered that RCT are the most suitable source of evidence for this assessment and considered 22 key RCTs for the NMA, excluding may analyses of real world data published in peer reviewed journals. Hence considering that the 29 stents are “comparable” is scientifically flaw, when for some of these stents no evidence that measures their safety and efficacy was factored in this draft assessment. Such a recommendation would put the patients’ safety at risk.	The wording of the recommendation regarding justification for price variation (recommendation 1.1) has been amended to say: There is not enough evidence comparing stents to determine whether price variation between different stents is justified.
6.	Consultee 2	3.4 RCTs are the most suitable source of evidence	The conclusion that the assessed stents are comparable in terms of clinical and cost effectiveness is misleading, not only for the clinical professionals decision making, but also for the patients’ safety and for the Commissioners when choosing the best value for money technology for the NHS ressources. In fact this LSA covers 29 drug eluting stents currently available through NHS Supply Chain. For 8 of the 29 stents there was no randomised and comparative evidence, and only 18 of the 29 stents had sufficient evidence to be included in the network metanalysis (NMA). The LSA considered that RCT are the most suitable source of evidence for this assessment and considered 22 key RCTs for the NMA,	Thank you for this comment. Please see response to comment number 5.

Comment no.	Consultee	Section no.	Comment	NICE response
			excluding may analyses of real world data published in peer reviewed journals. Hence considering that the 29 stents are “comparable” is scientifically flaw, when for some of these stents no evidence that measures their safety and efficacy was factored in this draft assessment. Such a recommendation would put the patients’ safety at risk.	
7.	Consultee 3	1.2 1 Recommendations	We find this statement too broad and inaccurate without the full context of the assessment methodology, and it risks misinterpretation in its current form. Though the evidence assessed did show broad comparability, only two outcome measures were considered (TLR and TVMI). The exclusion of important outcomes such as MACE, bleeding and others listed in the NICE scope increases the high degree of uncertainty as to whether the analyses are a reliable basis for decision-making. Indeed, the EAG called out the limitation of not capturing all relevant clinical outcomes in the NMA. We therefore propose an alternative recommendation here of: “Evidence on TLR and TVMI endpoints shows stents are comparable in terms of clinical and cost effectiveness, though other relevant endpoints could not be considered.”	Thank you for this comment. The guidance section ‘why the committee made these recommendations’ section now specifies the 2 outcomes for clarity. Please see also response to comment number 5. The external assessment group (EAG) noted that only two endpoints (TLR and TVMI) were considered, to enable the comparison of more devices in the NMA. The limitations of excluding other relevant endpoints in the analysis are outlined in the assessment report.

Comment no.	Consultee	Section no.	Comment	NICE response
8.	Consultee 3	1.3 Why the committee made these recommendations	We question the statement about clinical trial evidence showing similar clinical outcomes. In line with our previous comment, only two outcome measures were considered (TLR and TVMI). The exclusion of important outcomes such as MACE, bleeding and others listed in the NICE scope increases the degree of uncertainty around this statement, as highlighted in the EAG report.	Thank you for this comment. Please see responses to comment number 5 and 7.
9.	Consultee 4	1.2 1 Recommendations	We disagree with this wording of this recommendation as the evidence does not show that all stents are comparable. In the section named “It is uncertain whether some stents are more cost effective than others” on page 12, the following statement is made “There was a limited amount of evidence comparing effectiveness between the stents”. In addition, in section named “Justification for price differences” on page 15, the following statement is made, “The committee discussed the clinical and economic evidence overall. It concluded that it was not possible to determine whether the differences in cost between stents were justified by benefits derived from additional features.” We believe that these statement should make up the basis of this recommendation 1.2, as the current recommendation suggests that there is evidence showing that all the stents are comparable, which is not the case. The other point that is not made in these recommendations is that significant evidence exists for a some stents across all indications, both in the short and longer term and none in others. We do not agree that you can suggest that stents are comparable when some of the stents have very little evidence and none in certain indications.	Thank you for this comment. Please see response to comment number 5.

Comment no.	Consultee	Section no.	Comment	NICE response
10.	Consultee 4	3.4 RCTs are the most suitable source of evidence	We request you re-consider the inclusion of the 8 stents that do not have any randomised evidence comparing them with another stent in scope. We do not believe it is accurate to suggest these 8 stents are equal to the other stents without strong evidence backing this up.	Thank you for this comment. Please see response to comment number 5.
11.	Consultee 4	3.9 Results of the NMA are uncertain but suggest no difference in clinical outcomes	As there was only sufficient evidence to include 18 of the 29 stents in the NMA, we request you re-consider if these other 11 stents should still be included in the final publication. These stents were also not included in the economic model as a result, and this further emphasises the need to re-consider their inclusion in the guidance.	Thank you for this comment. Please see response to comment number 5.
12.	Consultee 4	3.14 It is uncertain whether some stents are more cost effective than others	We agree that there is “limited amount of evidence comparing effectiveness between stents” and therefore emphasize that the wording of recommendation 1.2 is misleading.	Thank you for this comment. Please see response to comment number 5.
13.	Consultee 4	3.21 Justification for price differences	The committee “concluded that it was not possible to determine whether the differences in cost were justified by benefits derived from additional features”. We agree with this synopsis and suggest that this wording would be a plausible inclusion for recommendation 1.2.	Thank you for this comment. Please see response to comment number 5.
14.	Consultee 6	Recommendation 1.2	Recommendation 1.2 states: “Evidence shows that stents are comparable in terms of clinical and cost-effectiveness, and that there is	Thank you for this comment.

Comment no.	Consultee	Section no.	Comment	NICE response
			no justification for price variation". The EAG stated that "the relative effect was too uncertain to establish any conclusions" (EAG report, page 14, para 2). and "economic findings are impacted by the underlying issue in the NMA" (page 16, bullet 5). and "this key source of uncertainty prevented a firm conclusion to be drawn" (page 16, bullet 5). In addition, the committee conclude: "because there is uncertainty about the cost effectiveness estimates, it is not possible to determine whether some drug-eluting stents are more cost-effective than others" (draft guidance, "why the committee made these recommendations", page 5 para 1). We therefore believe recommendation 1.2 is factually inaccurate, and we ask that recommendation 1.2 is reworded to better reflect the committee's conclusion and the limitations of the evidence review as outlined by the EAG. Proposed wording: "the EAG review was unable to determine whether stents were comparable in terms of clinical and cost effectiveness, nor were they able to determine whether there was justification for price variation".	Please see response to comment number 5.

Comment no.	Consultee	Section no.	Comment	NICE response
15.	Consultee 6	Not specified	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No, the summaries of the clinical and cost effectiveness evidence are not reasonable interpretations of the evidence because they do not reflect the serious limitations of the clinical and economic evaluations as highlighted by the EAG and the NICE Committee as outlined below: The overarching aim of this LSA is to demonstrate whether there is evidence of superior clinical effectiveness for any of the devices that justify a higher cost. The EAG highlighted serious limitations in the network meta-analysis (NMA) and economic findings as follows: • “the relative effect was too uncertain to establish any conclusions” (EAG report, page 14, para 2) • “Insufficient prior information to enable NMA model to estimate reliably” (EAG report, page 16, bullet 2) • “NMA using long-term data is highly dependent on the prior distribution, meaning the reliability of the estimate is a concern” (EAG report, (page 16, bullet 3) • “Economic findings are impacted by the underlying issue in the NMA, and this key source of uncertainty prevented a firm conclusion to be drawn” (EAG report, page 16, bullet 5). • “The economic results informed by the current evidence on treatment effect can have serious biases” (EAG report, page 132, para 3). In addition, the committee concluded: “because there is uncertainty about the cost-effectiveness estimates, it is not possible to determine whether some drug-eluting stents are more cost-effective than others” (draft guidance, page 5, para 1, “why the committee made these recommendations”).	Thank you for this comment. Please see response to comment number 5.

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			and “It is uncertain whether some stents are more cost-effective than others” (draft guidance page 12, section 3.14) Given that the EAG identified serious limitations of the clinical and economic evaluations, and that the NICE committee acknowledged the uncertainty about the cost-effectiveness estimates, the results from the EAG assessment cannot be considered reliable enough for committee decision making on the relative effectiveness or cost-effectiveness of the drug eluting stents in scope. We ask that the limitations of the EAG assessment and committee conclusions regarding the uncertainty of the cost-effectiveness evidence are clearly acknowledged in the recommendations section.	
16.	Consultee 6	Not specified	Are the recommendations sound and a suitable basis for guidance to the NHS? No, the recommendations are not a sound and suitable basis for guidance to the NHS for the following reasons: • EAG identified serious limitations in EAG analysis: o Not all stents had an RCT that was powered to assess clinical outcomes at a minimum follow-up of 1 year and so they were excluded from the NMA. o The NMA covered only 18 / 29 stents in the scope for the assessment (see Figure 1 Network plot and NMA forest plots, Committee Slides 20 and 22). As evidence relating to the 11 other stents is absent or has not been reviewed, conclusions regarding the efficacy of these stents and equivalence cannot be drawn.	Thank you for this comment. Please see responses to comments number 5, 7 and 17.

Comment no.	Consultee	Section no.	Comment	NICE response
			o The NMA included only 2 clinical outcomes. • The evidence in high-risk patients has not been reviewed, therefore conclusions cannot be assumed to apply to stents in these groups. • The committee concluded: “because there is uncertainty about the cost effectiveness estimates, it is not possible to determine whether some drug-eluting stents are more cost-effective than others” (“Why the committee made these recommendations” section and “Cost effectiveness” 3.14) • There are significant differences in the availability of clinical evidence and CE marked indications between stents, but this is not reflected in the recommendations.	

Theme 3. The least expensive stent

Comment no.	Consultee	Section no.	Comment	NICE response
17.	Consultee 3	1.3 1 Recommendations	We disagree with this statement. The term ‘least expensive’ implies that the product price alone is the sole economic contributor to its value. However, volume agreements and commitment deals may also play a role here. We request wording is amended to better reflect value for money rather than price alone.	Thank you for this comment. The guidance recommends (recommendation 1.2) that NHS trusts should provide access to a range of drug-eluting stents, so that a clinically appropriate stent is available for everyone with coronary artery disease.

Comment no.	Consultee	Section no.	Comment	NICE response
				The order of recommendations in the guidance document has been amended to make it clearer that the cost is a consideration (recommendation 1.3) that follows the consideration of having clinically appropriate stents available (recommendation 1.2). The guidance section 'What this means in practice' includes examples of factors that might make a stent more suitable: "When choosing a clinically appropriate drug-eluting stent, healthcare professionals should consider the patient, vessel and lesion characteristics, comorbidities and other factors that can make a stent more suitable." The following statements have also been added to the guidance section 'What this means in practice' to support

Comment no.	Consultee	Section no.	Comment	NICE response
				the importance of clinical and value considerations: “These recommendations are not intended to restrict choice. A clinically appropriate stent should be used, and if more than one is clinically appropriate then the least expensive should be used. This should be the stent that is the best value for the NHS trust” “These recommendations do not replace clinical reasoning.”
18.	Consultee 4	1.3 1 Recommendations	In the section named “Resource impact” on page 13, the following statement is made, “The committee recalled that the cost of the stents is a small part of the total procedure cost, and the price differences between stents are generally relatively small (see section 3.13). It was uncertain whether, in the context of the total spend on stents, these shifts would result in substantial savings.”. We agree with this statement and therefore suggest that the wording of “cheapest stent” is removed from the recommendations. We believe that it is a risk to include the wording of “cheapest stent”, especially as 11 of the 29 stents did not have enough evidence to be included in the NMA.	Thank you for this comment. Please see response to comment number 17.

Comment no.	Consultee	Section no.	Comment	NICE response
			As this guidance is aimed at procurement individuals, we believe there should be some guidance on what makes a stent "clinically appropriate". We believe that a large part of this guidance should be related to the level of evidence the stent has in the given vessel / lesion type.	
19.	Consultee 4	3.16 Resource impact	We agree that “the cost of the stent is a small part of the total procedure cost, and the price differences between stents are generally relatively small." We also agree that in the context of total spend, moving to a cheaper stent would not result in substantial savings and therefore do not think that the wording of “the cheapest stent” should be included in the recommendations. The recommendations should instead focus solely on the level of clinical appropriateness / evidence available for these stents.	Thank you for this comment. Please see response to comment number 17.
20.	Consultee 6	Recommendation 1.3	We ask that the wording in recommendation 1.3 “choose the least expensive stent” is amended to: “If more than one drug-eluting stent is available, use a stent that is clinically appropriate and represents value for money for the NHS”. This would be in line with the wording in the TAVI LSA recommendations.	Thank you for this comment. Please see response to comment number 17.
21.	Consultee 2	1.3 1 Recommendations	The definition of “clinically appropriate” should be better defined and specified. Many factors are considered when choosing the stent (i.e. complexity of the lesions, patient demographic, high bleeding risk….). The access for safe and effective stents that fit the patients’ clinical	Thank you for this comment. Please see response to comment number 17.

Comment no.	Consultee	Section no.	Comment	NICE response
			profile should be the priority and outweigh during the selection of the most fit for purpose stent.	

Theme 4. What information is needed

Comment no.	Consultee	Section no.	Comment	NICE response
22.	Consultee 2	1.3 What information is needed	The LSA considered that “RCT are the most suitable source of evidence” for this assessment and considered 22 key RCTs, excluding may analyses of real world data published in peer reviewed journals. Yet, it is surprising to see that in this paragraph secondary analysis of real-world data are needed to justify the price variation between different stents. We call to have more consistency between the type of studies and the ones that are actually factored in the assessment and inform the LSA recommendations. Given the choice of the stent depends on multiple parameters related to the patients’ profile (i.e. high bleeding risk, complexity of legion…), the following key outcomes should be added to the list as well: - Bleeding score - MACE Score (Major Adverse Cardiac Event - MACCE (Major Adverse Cardiac and Cerebrovascular Events) - Myocardial Infarction - NACE (Net Adverse Clinical Events) - Cardiac death.	Thank you for this comment. A clarification regarding the decision to not use the NICOR data has been added to the guidance section 3.3. The decision was made because the registry currently captures only a limited number of the stents and important confounders for this assessment, and health outcomes cannot always be linked back to individual stents or stent choice. The guidance section ‘What information is needed’ lists key outcomes and confounders that studies and analyses of real-world should

Comment no.	Consultee	Section no.	Comment	NICE response
			Comment on "Procurement and commissioning considerations": Bullet point #2: More specifics should be provided to clarify: - The nature of the “features”, - Whether this is referring to technical features, or to clinical safety/efficacy features, - And whether an RCT showing clinical superiority is methodologically relevant and proportionate to the associated new features. Bullet point #3: Many, if not the big majority of new generations of the stents bring technical iterations to the previous generation stent. Requesting an RCT showing non-inferiority when “minor improvements” are made to the new generation stents is methodologically irrelevant and disproportionate. Moreover this significantly hinders the access to innovation to the Patients and to the NHS. We request to delete completely this bullet point from the report.	account for. This section has been amended to clarify that the information that is needed to justify price variation can be from primary studies or secondary analyses of real-world data that compare different stents. Please see also response to comment number 24.

Theme 5. What this means for procurement and commissioning

Comment no.	Consultee	Section no.	Comment	NICE response
23.	Consultee 3	3.16 Resource impact	"It was uncertain whether, in the context of the total spend on stents, these shifts would result in substantial savings." We believe this is an important statement and this context should be highlighted in the “what this means in practice” section for procurement and	Thank you for this comment. The committee discussion on potential resource impact is described in guidance section

Comment no.	Consultee	Section no.	Comment	NICE response
			commissioning, in order to manage expectations and avoid unnecessary disruption.	3.16. NICE may publish resource impact tools or summaries alongside its guidance.
24.	Consultee 2	3.22 Evidence needed to show additional value	We believe the clinical studies and the design needed should be relevant to the research questions and the added value a new stent is bringing. Requesting to have an RCT showing clinical superiority can be methodologically irrelevant and disproportionate in some situations. We suggest to replace the sentence "This would ideally be from an RCT designed to show the clinical superiority of a stent" as follows: "The type and design of the study will depend on the research question that it is addressing and the outcomes that are measured". Many, if not the big majority of new generations of the stents bring technical iterations to the previous generation stent. Requesting an RCT showing non-inferiority when "minor improvements" are made to the new generation stents is methodologically irrelevant and disproportionate. Moreover this significantly hinders the access to innovation to the Patients and to the NHS. We request to delete completely this sentence from the report: "If a company introduces to the market a new drug-eluting stent or a new generation of the technology with minor improvements, it should show clinical non-inferiority".	Thank you for this comment. The text about what evidence is needed for new stents or stent features in the guidance section with commissioning and procurement considerations has been amended to say: "If a company introduces a new drug-eluting stent or a new stent feature with a higher price to the market, they should provide evidence to justify price variation."
25.	Consultee 4	1.3 What information is needed	We request clarity on the level of evidence expected in the non-inferiority studies for the new generations of stents. We do not believe it is a feasible ask to expect industry to support / fund	Thank you for this comment.

Comment no.	Consultee	Section no.	Comment	NICE response
			evidence generation to show non-inferiority of new generations of stents if there has been minimal changes made.	Please see response to comment number 24.

Theme 6. What this means for healthcare professionals

Comment no.	Consultee	Section no.	Comment	NICE response
26.	Consultee 3	1.3 What information is needed	With regards to 'what this means in practice', we support these recommendations for HCPs, and the recognition of the importance of a range of stents to treat the variable nature of lesions.	Thank you for this comment.
27.	Consultee 6	What this means in practice - Healthcare professional consideration, lines 15-18	”What this means in practice” section states: “When choosing a clinically appropriate drug-eluting stent, healthcare professionals should consider the patient, vessel and lesion characteristics, comorbidities and other factors that can make a stent more suitable”. As NICE methods do not recommend technologies outside the terms of the technology’s regulatory approval and CE mark indications vary between devices (www.nice.org.uk/process/pmg36), we ask that further guidance around “clinically appropriate” is added to this statement to avoid the risk of patients being exposed to stents that do not have CE mark for their specific patient characteristics. This is particularly important for high-risk patients such as patients with high bleeding risk as “suitability for people having abbreviated 1-month dual antiplatelet therapy (DAPT)” was highlighted as a patient level and contract level criteria in the user preference report; definition: Stent has clinical evidence for safety in people (with high bleeding risk having abbreviated 1-month DAPT (user preference	Thank you for this comment. The guidance section 2.2 describes the technologies and says that the indications for use vary and may specify subpopulations or lesion types. People with high risk of bleeding were assessed as one of the subgroups. Committee’s considerations on subgroup data are in guidance sections 3.7 and 3.8. The sections 3.18 to 3.20 describe committee’s equality

Comment no.	Consultee	Section no.	Comment	NICE response
			report, tables 2 & 3). Proposed wording: “When choosing a clinically appropriate drug-eluting stent, healthcare professionals should consider the patient, vessel and lesion characteristics, comorbidities and other factors that can make a stent more suitable. CE mark indication and robust clinical evidence in those indications should be key considerations when choosing a clinically appropriate drug-eluting stent”.	considerations. People with high risk of bleeding have been added in these considerations. People with high risk of bleeding have been also added as a population in the equalities impact assessment document. Please see also response to comment number 17.
28.	Consultee 6	What this means in practice - Healthcare professional considerations, bullet 5.	”What this means in practice” section states: “Healthcare professionals should work with commissioners and procurement specialists in their NHS trust to ensure access to a range of stents”. NICE methods state that NICE does not recommend technologies outside the terms of the technology’s regulatory approval and CE mark indications vary between devices (NICE health technology evaluations: the manual (PMG36), page 38, 2.2.6. www.nice.org.uk/process/pmg36), we ask that further guidance is added to this statement to avoid the risk for patients being exposed to stents that do not have CE mark for their specific patient characteristics. This is particularly important for high-risk patients such as patients with high bleeding risk, left main and bifurcation. Proposed wording: “Healthcare professionals should work with commissioners and procurement specialists in their NHS trust to ensure access to a range of stents. CE mark indication and robust clinical evidence in those indications should be key considerations in	Thank you for this comment. Please see responses to comments number 17 and 27.

Comment no.	Consultee	Section no.	Comment	NICE response
			commissioning and procurement decisions on selecting a “clinically appropriate range of drug-eluting stents”.	
29.	Consultee 4	1.3 What information is needed	We agree with both points made here as they support clinical appropriateness and equity of access. Having said this, we also suggest that the level of evidence should be included in these considerations as some stents have evidence in a wide range of vessel / lesion types and others do not.	Thank you for this comment. Please see responses to comments number 17 and 27.
30.	Consultee 4	1.3 What information is needed	We would like to emphasize that clinical appropriateness can only be shown by robust and sufficient clinical evidence. The amount of data generated and invested in by the companies is a testimonial to the clinical effectiveness of the stent and the lack thereof should not be compensated by the acceptance of low cost.	Thank you for this comment. Please see responses to comments number 17 and 27.

Theme 7. Network meta-analysis

Comment no.	Consultee	Section no.	Comment	NICE response
31.	Consultee 2	3.8 Results of the NMA are uncertain but suggest no difference in clinical outcomes	We would request to have more details about the NMA in order to mitigate the major follow-up timeframe difference in the analysis on one hand and have a clarification of the relative treatment effect outlier figures calculated on the other hand. This can only bring more transparency and build a sound comparison approach. Separately, having in mind the limitations of the NMA highlighted by the report, building a recommendation on a NMA which presents	Thank you for this comment. The guidance section 3.9 describes committee’s considerations of the network meta-analysis results. The committee noted that results were uncertain and the external assessment group

Comment no.	Consultee	Section no.	Comment	NICE response
			very high uncertainty results will result in misleading conclusions, ultimately bias the decision making process and the quality of the care delivered to the patients putting their life at risk. Only 18 of the 29 stents had sufficient evidence to be included in the NMA. The LSA considered that RCT are the most suitable source of evidence for this assessment and considered 22 key RCTs for the NMA, excluding may analyses of real world data published in peer reviewed journals. Hence considering that the 29 stents are "comparable" is scientifically flaw, when for some of these stents no evidence that measures their safety and efficacy was factored in this draft assessment. Such a recommendation would put the patients' safety at risk.	(EAG) explained that having only limited data for each comparison in the analysis, even less so for the exploratory long-term analysis, was a key reason for the uncertainty. Using evidence from predecessor stents may have added uncertainty to the results. The word "exploratory" has been added in front of the word "long-term analysis" to emphasise the exploratory nature of the long-term analyses.
32.	Consultee 6	3.8	The header for section 3.8 states: "Results of the NMA are uncertain but suggest no difference in clinical outcomes" The EAG stated that "the relative effect was too uncertain to establish any conclusions" (EAG report, page 14, para 2) therefore it is factually incorrect to state "Results of the NMA are uncertain but suggest no difference in clinical outcomes". We ask that this section header statement is removed from section 3.8 to avoid misrepresentation of the EAG conclusion that "the relative effect was too uncertain to establish any conclusions" (EAG report, page 14, para 2).	Thank you for this comment. The section header for the guidance section 3.9 has been amended to "Results of the NMA are uncertain".

Theme 8. User preferences

Comment no.	Consultee	Section no.	Comment	NICE response
33.	Consultee 5	Not specified	This guidance does not account for clinician choice regarding the thickness of stent struts, depending on clinical presentation. Physical characteristics such as strut thickness aid stent deliverability, particularly in tortuous lesions. The thinner the struts, the lower the crimped stent profile, hence it can pass through tighter stenoses. While other physical characteristics, such as stent length, are accounted for, it should be noted that there is a wide range of characteristics impacting clinician choice beyond those currently mentioned in the draft guidance.	Thank you for this comment. The clinical experts noted that user preference assessment participants considered physical stent characteristics as part of deliverability. Please see also response to comment number 17.

Theme 9. Subgroups

Comment no.	Consultee	Section no.	Comment	NICE response
34.	Consultee 6	Recommendation 1.2	We are concerned that generalisation of conclusions regarding relative treatment effects to this high-risk group could drive poorer outcomes for high-risk patients if clinically appropriate stents were unavailable as an option due to the flawed assumption that there is no difference in efficacy between stents in all groups. We ask the committee to note that only 18/29 currently available stents were included in the network meta-analysis and to acknowledge in the recommendations section that there are	Thank you for this comment. Please see responses to comments number 5 and 27.

Comment no.	Consultee	Section no.	Comment	NICE response
			significant differences in CE marked indications and evidence base between stents.	
35.	Consultee 6	Not specified	Has all of the relevant evidence been taken into account? No, the EAG excluded trials in high-risk patients from the network meta-analysis (NMA) and economic evaluation, and a separate qualitative review of the evidence for high-risk groups was not conducted. This means that the evidence for a significant proportion of patients in these high-risk categories are excluded, e.g. up to 40% of patients are at high bleeding risk, ~30% of PCI involve a bifurcation, more than 80% of left main disease involves the bifurcation, and left main coronary artery (LMCA) disease is discovered in 5-8% of patients undergoing coronary angiography. Evidence in these high-risk groups has not been assessed by the EAG therefore conclusions and recommendations cannot be assumed applicable to high-risk populations. We ask the committee to note the substantial body of evidence in high-risk groups, that is only available for certain stents, was excluded from the EAG review, including the studies below and ask that these significant limitations are clearly acknowledged in the recommendations section. One RCT data in high bleeding risk patients (Onyx ONE) was identified in the EAG evidence review but this was excluded from the NMA and not adequately reviewed elsewhere. The EAG appears to have excluded all the data that do not compare different stent technologies, such as EBC MAIN trial in left main lesions (Hildick-Smith 2021) and KISS trial in bifurcation lesions (Chevalier 2023). While they do not compare different stent technologies, “clinical experts indicated that the volume of clinical efficacy evidence available for specific stents and whether there is evidence of clinical efficacy and safety in particular populations (e.g., high bleeding risk),	Thank you for this comment. The external assessment group (EAG) noted that the network meta-analysis and subsequent economic analysis did not include subgroup analyses of high-risk groups due to insufficient evidence. The following clarification has been added to the guidance section 3.9: “There was even less data available comparing stents in the subgroup populations, so it was not possible to do an NMA for the subgroups. The committee recalled that, in the subgroup data that was available for women and for people with left main-stem lesions, bifurcation lesions, high risk of bleeding or diabetes, these characteristics had no significant effect on the

Comment no.	Consultee	Section no.	Comment	NICE response
			could be useful for decision making" (EAR Report p77, para 3). High-bleeding risk • Windecker (2020) Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk (Onyx ONE Trial) https://www.nejm.org/doi/09.1056/NEJMoa191002 • Windecker (2022) Polymer-Based Versus Polymer-Free Stents in High Bleeding Risk Patients: Final 2-Year Results From Onyx ONE https://pubmed.ncbi.nlm.nih.gov/35680195/ • Kandzari (2020) One-month dual antiplatelet therapy following percutaneous coronary Intervention with Zotarolimus-eluting stents in high-bleeding-risk patients. (Onyx ONE Clear Trial) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7665241/ • Kandzari (2021) One-Month Dual Antiplatelet Therapy After PCI With Resolute Onyx DES: Final 2-Year Results From Onyx ONE Clear. https://doi.org/09.1016/j.jacc.2021.08.885 Left main lesions • Hildick-Smith (2021) The European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBC MAIN) https://pubmed.ncbi.nlm.nih.gov/34002215/ • Hildick-Smith (2023) The European Bifurcation Club Left Main Coronary Stent Study - A Randomized Comparison of Stepwise Provisional versus Systematic Dual Stenting Strategies (EBC Main) 3-year results. https://media.pcronline.com/diapos/EuroPCR2023/86-20230516_1655_Room_Maillot_Hildick-Smith_David_1111100_(10139)/Hildick-Smith_David_20230516_1645_Room_Maillot.pdf • Tarantini (2023) A large, prospective, multicentre study of left main PCI using a latest-generation zotarolimus-eluting stent: the ROLEX	clinical outcomes (see guidance section 3.7)." The EAG clarified that it prioritised the evidence it believes to be most relevant to the decision problem (in other words, comparative RCTs). The pragmatic approach taken by the EAG is permitted under the NICE LSA interim methods and processes. The guidance section 3.4 explains that the committee agreed that RCTs were the most suitable source of evidence for this assessment. But that the committee acknowledged that there was a large volume of other types of evidence (14 non-randomised or observational comparative studies and 54 single-arm studies) related to the stents in scope. The EAG noted that the EAG report executive summary states that there was a lack of

Comment no.	Consultee	Section no.	Comment	NICE response
			study. https://eurointervention.pcronline.com/doi/09.4244/EIJ-D-22-00454 • Tarantini (2023) A large, prospective, multicentre study of left main PCI using a latest-generation zotarolimus-eluting stent: the ROLEX study 2-year results. https://media.pcronline.com/diapos/EuroPCR2023/86-20230516_1647_Room_Maillot_Tarantini_Giuseppe_1111100_(10136)/Tarantini_Giuseppe_20230516_1645_Room_Maillot.pdf Bifurcation lesions • Chevalier (2023) Keep bifurcation stenting simple (KISS) Trial 1-month results. https://media.pcronline.com/diapos/EuroPCR2023/1263-20230516_1213_Room_Maillot_Chevalier_Bernard_1111100_(8747)/Chevalier_Bernard_20230516_1200_Room_Maillot.pdf • Chevalier (2024) Keep bifurcation stenting simple (KISS) Trial 1-year results. https://media.pcronline.com/diapos/EuroPCR2024/87-20240515_1632_Theatre_Havane_Chevalier_Bernard_1111100_(669)/Chevalier_Bernard_20240515_1630_Theatre_Havane.pdf • Price (2021) ONE YEAR CLINICAL OUTCOMES IN PATIENTS WITH CORONARY BIFURCATION LESIONS: RESULTS FROM THE RESOLUTE ONYX BIFURCATION STUDY (Post-Approval Study). https://www.jacc.org/doi/09.1016/S0735-1097%2821%2902324-X • Price (2022) Two-Year Outcomes in Patients with Bifurcation Lesions treated with Resolute ONYX ZES: Final Results from the RESOLUTE ONYX Bifurcation Study. https://doi.org/09.1016/j.jscai.2022.100132 • Price (2023) The Resolute Onyx Bifurcation Study: 3-Year Outcomes in Patients with Coronary Bifurcation Lesions.	evidence to suggest differences in outcomes between any stents in the subgroups identified in the scope. Where RCTs reported results for particular subgroups, or where subgroup analyses were reported, no significant differences in between-stent clinical outcomes were observed within that subgroup (see also EAG report section 5.1.2 and Appendix E, the subgroup information in the assessment is also summarised in section 'Data on subgroups' on page 8 of the assessment report overview). The committee's considerations on subgroup data are described in guidance section 3.7 and 3.8. Please also see responses to comments number 5 and 27.

Comment no.	Consultee	Section no.	Comment	NICE response
			https://doi.org/09.1016/j.jscai.2023.100736 • Hildick-Smith (2021) The European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBC MAIN) https://pubmed.ncbi.nlm.nih.gov/34002215/ • Hildick-Smith (2023) The European Bifurcation Club Left Main Coronary Stent Study - A Randomized Comparison of Stepwise Provisional versus Systematic Dual Stenting Strategies (EBC Main) 3-year results. https://media.pcronline.com/diapos/EuroPCR2023/86-20230516_1655_Room_Maillot_Hildick-Smith_David_1111100_(10139)/Hildick-Smith_David_20230516_1645_Room_Maillot.pdf Limited number of stents reviewed in NMA • The NMA covered only 18 / 29 stents in the scope for the assessment (see Figure 1 Network plot and NMA forest plots, Committee Slides 20 and 22). As evidence relating to the 11 other stents is absent or has not been reviewed, conclusions regarding the efficacy of these stents and equivalence cannot be drawn.	
36.	Consultee 6	Not specified	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? We are concerned that generalisation of conclusions regarding relative treatment effects to this high-risk group, without regard to the significant differences in clinical evidence and CE marked indications between stents, could drive poorer outcomes for high-risk patients if clinically appropriate stents were unavailable as an option, due to the flawed assumption that there is no difference in efficacy evidence between stents in all groups.	Thank you for this comment. Please see responses to comments number 5, 27 and 35.

Comment no.	Consultee	Section no.	Comment	NICE response
37.	Consultee 6	Recommendation 1.2	In addition to the uncertainty in the clinical and economic findings as outlined in the comment above, we ask that an additional statement is added in recommendation 1.2 to reflect that the EAG assessment excluded trials that included only high-risk patients from the network meta-analysis (NMA) and did not conduct a separate qualitative evidence review of the evidence for high-risk groups. People with high bleeding risk, left main stem lesions and bifurcation lesions were identified as relevant subgroups in the scope however the evidence base for these groups has not been assessed therefore conclusions or recommendations based on the limited network meta-analysis cannot be assumed to be applicable to high-risk populations. NB: A significant proportion of patients are in these high-risk categories e.g. up to 40% of patients are at high bleeding risk, ~30% of PCI involve a bifurcation, more than 80% of left main disease involves the bifurcation and left main coronary artery (LMCA) disease is discovered in 5-8% of patients undergoing coronary angiography. Given the lack of review of the evidence in high-risk groups we ask the committee to add a comment to recommendation 1.2 indicating that “no comparisons or conclusions can be drawn regarding the relative efficacy or relative cost effectiveness of stents in high-risk groups”, as this was not reviewed.	Thank you for this comment. The committee considered the individual trials comparing stents including those where a subgroup in the scope was the main population. Please see also responses to comments number 5, 27 and 35.
38.	Consultee 6	3.6, para 1	Clinical effectiveness section 3.6 states: “None of the subgroup characteristics had a significant effect on the clinical outcomes. The committee heard from clinical experts that this was reflective of their experience”.	Thank you for this comment. The sentence “The committee heard from clinical experts

Comment no.	Consultee	Section no.	Comment	NICE response
			We believe that this statement does not accurately reflect the committee discussions or user preference report, where experts described the difference between stents in evidence base and compatibility for shorter DAPT in high bleeding risk patients in particular. The EAG report states: “With respect to clinical decision making, clinical experts indicated that clinical efficacy, as measured by incidence of clinical events, are the key decision-making factors when selecting a type of DES. However, other factors such as co-morbidities may also influence choice. In particular, in people who are considered of high-bleeding risk, there would be preference for a device that has evidence to demonstrate compatibility with shorter DAPT regimens. The EAG identified some evidence of shorter DAPT regimens being safe in conjunction with some of the stents in scope, but as a systematic review into this aspect of the care pathway was not conducted, definitive conclusions cannot be made with respect to safety of shorter DAPT in conjunction with any of the devices in scope” (P133, para 1, EAG report). We ask that this statement is amended to reflect the experts’ experience that other factors such as co-morbidities may also influence choice and their preference for a device that has evidence to demonstrate compatibility with shorter DAPT regimens for people who are considered at high bleeding risk, as outlined in the EAG report.	that this was reflective of their experience.” has been removed from the guidance section 3.7. Please see also responses to comments number 5, 27 and 35.