National Institute for Health and Care Excellence

IP881/2 Percutaneous transarterial carotid artery stent placement for asymptomatic extracranial carotid stenosis

IPAC date: 14 September 2023

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Company TERUMO EUROPE	Specific questions for consultation (see end of table)	We have extensively responded to Question 2 in our "Draft recommendations" comments. We do not understand Question 3. Indeed the 9 major studies included in the Overview were published 2015-2023, most of them between 2021-2023, so very recent evidence, giving a very up-to-date picture of the evidence, is available.	Thank you for your comment. Although the systematic reviews were published between 2020 and 2023, they included studies that were published between 1990 and 2021.
2	Consultee 2 Company Medtronic Ltd	Specific questions for consultation (see end of table)	1. Medtronic believe that if a permissive recommendation is published, then an increase in imaging may be seen, however this would be independent of the recommendation. Recent studies have found that lesion imaging is an excellent predictor of risk for a patient and is important in assessing the appropriate therapy (medicinal or surgical). 2. Yes, Medtronic believe that the conclusions made within the draft guidelines and clinical overview based on the literature review does reflect the breadth and quality of the available evidence. 3. The paper found in the evidence review, Kim et al (2023), is a thorough summary of medicinal and surgical management. As noted from Kim et al, evidence suggests that the rate of stroke with medical therapy is approximately 1% per year. Assessment of risk via imaging, along with a patient's demographics, would provide direction on	Thank you for your comment. Consultee agrees with main recommendation. The review by Kim et al. (2023) is included in table 5 of the overview.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			whether surgical intervention or medicinal therapy is appropriate for a given patient. Reference: Kim HW, Regenhardt RW, D'Amato SA, et al Asymptomatic carotid artery stenosis: a summary of current state of evidence for revascularization and emerging high-risk featuresJournal of NeuroInterventional Surgery 2023;15:717-722. 4. Medtronic is not aware of long-term complications related to stents beyond 10 years that are different from those present (type and rate) within the first ten years. Long term disease management will exceed ten years that may require additional therapeutic intervention.	
3	Consultee 3 Specialist society BSNR	Specific questions for consultation (see end of table)	1. The current recommendations are unlikely to impact on imaging services but there is potential if this procedure became more widely available there would be call for increased imaging to "screen" for asymptomatic extrancranial carotid stenosis. This is of concern to already overstreched and understaffed imaging services. 2. The BSNR membership are in support of the committee's interpretation of the evidence although it has been commented that a number of trails are ongoing at the moment and some members suggested awaiting the results of the trials should be made before publishing guidance. 3. BSNR membership did not comment on this but implied the results of ongoing trials should be awaited which could potentially provide new evidence. 4. The evidence for this remains unclear.	Thank you for your comment. The consultee agrees with main recommendation but notes that there are a number of ongoing trials. The consultee has subsequently confirmed that the completion dates have been extended. There was a substantial amount of new evidence published since the original guidance was produced, including the results of the ACST-2 trial, which was named in the guidance. Although there are a number of ongoing trials listed in the overview, none of them are

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
				estimated to complete within the next year.
4	Consultee 1 Company TERUMO EUROPE	1.1	We would like to thank NICE and the IP Advisory Committee for the opportunity to provide our comments to this draft guidance. We do acknowledge that the used methodology and the evidence overview reflect state of the art knowledge related to the subject of CAS. However, we disagree with the resulting recommendation and the conservation of “Special arrangements”, instead of "Standard arrangements". We believe that this recommendation is not correctly reflecting the outcomes of the large body of evidence available in this field. Since the previous guidance, landmark RCTs (such as ACST-2) and numerous systematic reviews and meta-analyses have been published and we are disappointed to read the Committee’s comment that “there is still uncertainty about this procedure’s use in asymptomatic extracranial carotid stenosis”. To use just one example, we would like to quote some paragraphs from the ACST2 trial, an RCT (LEVEL 1 evidence): “The main finding from the ACST-2 trial of CAS versus CEA is that the effects of the two procedures on disabling or fatal events are approximately equal in terms of procedural hazards (about 1% for each treatment, in line with findings from large, representative registries) and of 5-year disabling stroke rates (which were about 0·5% per year with either procedure, suggesting that they would have been about 1% per year with neither procedure).” This conclusion of the ACST-2 trial suggests that major complications are equally rare with either CAS or CEA and that both procedures essentially halve the annual risk relative to best medical treatment. “With ACST-2 included, there is now as much evidence among asymptomatic as among symptomatic patients, and the findings in both types of patient are remarkably similar, with CEA slightly but non-	Thank you for your comment. Consultee disagrees with main recommendation and highlight the results of the ACST-2 trial (Halliday et al., 2021), which are included in the key evidence. The committee noted that the ACST-2 trial did not directly compare CAS with medical treatment. The committee discussed this comment but considered there is still too much uncertainty about the benefits of the procedure in asymptomatic patients for it to be used under standard arrangements.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			significantly better than CAS, at least for non-disabling stroke. Overall, the ratio (CAS vs CEA) of long-term stroke incidence rates is 1·11 (95% CI 0·91–1·32; p=0·21). As previous studies have shown successful CEA to be substantially protective,4,5 this RR of 1·11 (which includes the ACST-2 result) shows that the protective effects of CAS and CEA are similar for at least the first few years." This conclusion of the ACST-2 trial suggests that there is currently equal amount of evidence for symptomatic and asymptomatic patients and that in both populations the findings are remarkably similar, in both cases showing that protective effects of CAS and CEA are comparable for at least few years. In contrast, NICE has recommended "Standard arrangements" for CAS in symptomatic patients since 2011 (IPG389). Therefore we would strongly argue for a similar recommendation for asymptomatic patients. We have looked carefully at the definition of "Special Arrangements": This means that there are uncertainties about whether a procedure is safe and effective. We also recommend special arrangements if risks of serious harm are known. These will need to be carefully explained to a patient before they make a decision. A special arrangements recommendation places emphasis on the need for informed consent. This includes both the patient (or carer) and senior medical staff, such as the clinical governance lead in their trust. Clinicians using these procedures should collect data, either by audit or research. If there's no method of data collection already available, we'll publish an audit tool along with the guidance." We don't believe that any of the above points apply to the available evidence for the treatment of asymptomatic patients. The Committee adds that evidence > 10 years is lacking. We do not think it is available for CAS in symptomatic patients (IPG389) nor for	

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			Transcervical extracorporeal reverse flow neuroprotection for reducing the risk of stroke during carotid artery stenting (IPG561), both of which have received a "Standard Arrangements" recommendation. Therefore we would argue for a "Standard arrangements" recommendation for asymptomatic patients.	
5	Consultee 2 Company Medtronic Ltd	1	Medtronic believe that the recommendation for this procedure to remain in “special arrangements” is largely robust, however, the rationale supporting the recommendations (specifically within the draft guidelines) does not highlight the clear risks associated with conventional surgery for high-risk patients. It is of clinical importance to highlight the use of “Transfemoral carotid artery stent placement” as an alternative procedure for patients diagnosed with asymptomatic extracranial carotid stenosis who may be unsuitable for a carotid endarterectomy (CEA). For patients that are contraindicated for general anesthesia or high risk for more invasive procedures, less invasive procedures such as stenting may present reduced risk of complications. This view is supported by section 2.5 of the draft guidelines, “Carotid stenting is a less invasive percutaneous alternative to CEA. Potential advantages include the avoidance of general anaesthesia and the need for a neck incision that may result in cranial and cutaneous nerve damage. The rate of general surgical complications such as myocardial infarction may also be reduced”. Therefore, we would kindly request that the committee amend the wording within the section “Why the committee made these recommendations”, to account for the high-risk patients. We have suggested the wording below, as this may appropriately capture all	Thank you for your comment. The consultee suggests that the risks associated with conventional surgery for some people should be highlighted and that this procedure should be an option when CEA is unsuitable. Section 2.5 of the draft guidance currently states: ‘Carotid stenting is a less invasive percutaneous alternative to CEA. Potential advantages include the avoidance of general anaesthesia and the need for a neck incision that may result in cranial and cutaneous nerve damage. The rate of general surgical complications such as myocardial infarction may also be reduced.’

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			patient groups: “There is still uncertainty about this procedure’s use in asymptomatic extracranial carotid stenosis. Short-term evidence suggests that the risk of disabling stroke is similar in people who have this procedure compared with people who have conventional surgery. However, more long-term evidence beyond 10 years is needed. It is also uncertain how well the procedure works compared with current standard medical therapy. This procedure can be used for patients who may be considered unsuitable for conventional surgery. Overall, more research is needed to identify which people might benefit from this procedure.”	
6	Consultee 2 Company Medtronic Ltd	1.1	Medtronic thank NICE for the opportunity to respond to the draft recommendations for the interventional procedure guideline for transfemoral carotid artery stent placement for asymptomatic extracranial carotid stenosis. Medtronic agree with draft recommendation 1.1, stipulating that this procedure should remain in “special arrangements”, based on the committee’s conclusion that “there is still uncertainty about this procedure’s use in asymptomatic extracranial carotid stenosis.”	Thank you for your comment. Consultee agrees with main recommendation.
7	Consultee 3 Specialist society BSNR	1	The guidance based on the current evidence is satisfactory but it has been noted that a number of trials are ongoing and it has been suggested by the BSNR membership that it may be worth awaiting the outcomes of these trials - some of which are due for completion within 12 months - would increase the evidence for developing guidance.	Thank you for your comment. The consultee agrees with main recommendation but notes that there are a number of ongoing trials. The consultee has subsequently confirmed that the trials are no longer due for completion within 12 months.

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8	Consultee 4 Specialist society Association of British Neurologists	1	I note the draft recommendations 1.1 to 1.7 and in particular recommendation 1.1 which states that the intervention should be used only with special arrangements for clinical governance, consent, and audit or research. I note the definition given of special arrangements: This means that there are uncertainties about whether a procedure is safe and effective. We also recommend special arrangements if risks of serious harm are known. These will need to be carefully explained to a patient before they make a decision. A special arrangements recommendation places emphasis on the need for informed consent. This includes both the patient (or carer) and senior medical staff, such as the clinical governance lead in their trust. Clinicians using these procedures should collect data, either by audit or research. If there's no method of data collection already available, we'll publish an audit tool along with the guidance. In view of the uncertainties described about the risks and harms of this procedure there is clearly a strong case for a large randomised controlled trial to compare the long term outcomes, particularly as best medical therapy with lifestyle advice, control of blood pressure, smoking cessation and other pharmacological interventions will have proven benefits which are not confined to one asymptomatic artery. If enrolment in to a suitably powered trial is not a viable option (I note the problems described with recruitment in some of the trials quoted) for all patients then the "special arrangements" suggested seems a reasonable compromise.	Thank you for your comment. Consultee agrees with main recommendation.
9	Consultee 2	2.2	It is important for the committee to consider the inclusion of “clinical imaging” within the draft guidance. This is currently standard practice	Thank you for your comment.

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	Company Medtronic Ltd		and clinical imaging is performed in order to: 1. Identify the clinical risk to the patient, 2. Inform what procedure would be most beneficial towards treating the patient (CEA or stent placement), and 3. Indicate when to intervene (review plaque location and size). Therefore, we would kindly request that the committee include additional wording within the section “The procedure”, to document existing clinical practice. We have suggested the wording below, as this may appropriately capture all patient groups: “Clinical imaging should be used as part of standard practice to identify the clinical risk and suitability of this procedure for asymptomatic patients.”	The procedure description has been changed to state that it is usually done after imaging.
10	Consultee 1 Company TERUMO EUROPE	2.3	We would strongly support a mention of the increasing adoption of the transradial access (instead of transfemoral) into general CAS practice. Recent evidence shows promising long-term results (Petkoska D. et al, Radial and ulnar approach for carotid artery stenting with Roadsaver™ double layer micromesh stent: Early and long-term follow-up. Catheter Cardiovasc Interv. 2023;101:154–163). Moreover, as per the pan-European ROADSAVER study data (NCT03504228 https://www.clinicaltrials.gov/study/NCT03504228?term=ROADSAVER&rank=1 ; publication in preparation), the radial route seems to be used in about 25% of all CAS cases treated as per standard of care, which in our humble opinion warrants at least a mention of this alternative access as a legitimate alternative delivery technique in CAS.	Thank you for your comment. ‘Transfemoral’ has been removed from the title and a sentence has been added to section 2.3 of the draft guidance, to note that transradial access has also been used. The cited study has not been included in the overview because it is an observational study with fewer than 1,000 patients.
11	Consultee 3 Specialist society BSNR	2	No additional comments for the BSNr membership	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
12	Consultee 3 Specialist society BSNR	3.6	This is the only point the BSNR membership really commented upon and questioned why the results of the ongoing trials were not awaited before proceeding to developing guidance.	Thank you for your comment. Although there are a number of ongoing trials listed in the overview, none of them are estimated to complete within the next year.
13	Consultee 1 Company TERUMO EUROPE	3.7	We do appreciate that NICE has recognized the progress in the field and has highlighted the fact that there are now more modern tools and techniques. We, however, would suggest that the final recommendation also includes a clarification regarding the specific tools and techniques that have in the meantime been developed to improve the safety and efficacy of CAS. Here we would suggest to explicitly mention the development of dual-layer micromesh stents. We believe that it is crucial to acknowledge the specific progress made in the field as, in addition to improved operator competence, the development of modern tools and techniques has contributed to improved safety and efficacy of the CAS procedure over the past 2 decades.	Thank you for your comment. Section 3.7 has been changed to note that stent design has changed over time.
14	Consultee 3 Specialist society BSNR	3.8	The BSNR support this statement in there remains uncertainty for intervention in asymptomatic carotid stenosis.	Thank you for your comment.
15	Consultee 2 Medtronic Ltd Company	General	Medtronic believe that the conclusions made within the draft guidelines and clinical overview based on the literature review does reflect the breadth and quality of the available evidence. However, it is important to review additional clinical evidence that may not have been considered. We ask that the following published studies be included in the review.	Thank you for your comment. The cited reference was not identified in the literature search because it does not mention carotid artery stenting. It has been added to table 5. The paper concludes that high-risk plaques

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			Complications associated with high-risk plaques - Kamtchum et al conducted a meta-analysis of 64 studies that enrolled 20,751 participants and found that high-risk plaques were common in patients with asymptomatic carotid stenosis, and the associated annual incidence of ipsilateral ischemic events (4 events per 100 person-years) was higher than the currently accepted estimates. The most prevalent high-risk plaque features were neovascularization, echolucency and lipid-rich necrotic core. Reference: Kamtchum-Tatuene J, Noubiap JJ, Wilman AH, Saqqur M, Shuaib A, Jickling GC. Prevalence of High-risk Plaques and Risk of Stroke in Patients With Asymptomatic Carotid Stenosis: A Meta-analysis. JAMA Neurol. 2020;77(12):1524–1535. doi:10.1001/jamaneurol.2020.2658	were common in patients with asymptomatic carotid stenosis, and the associated annual incidence of ipsilateral ischemic events (4 events per 100 person-years) was higher than the currently accepted estimates.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."

Note: The following questions were included in the consultation documents to target consultee responses:

1. Is it likely that a more permissive recommendation would lead to increased demand for evaluation of carotid artery stenosis? If so, what would the effects be on the health service (both imaging services and vascular surgical services)?

2. Do you agree with the committee's interpretation of the evidence?

3. Many of the papers in the evidence review were written some time ago. Have more recent advances in the medical management of asymptomatic carotid artery stenosis reduced the need for surgical interventions, such as the use of stents?

4. Are outcomes from stents affected by long-term complications, such as restenosis or stroke occurring after 10 years, or would any difference in outcomes between stenting and continued medical management be seen within 10 years.