

Approvals and indications of CGRP antibodies

We would like to clarify the various approval statuses of the calcitonin gene-related peptide (CGRP) antibodies mentioned in your Editorial, "Complicated decisions on new migraine-prevention therapies."¹ The Editorial should have stated that all three of the CGRP antibodies (erenumab, galcanezumab, and fremanezumab) are approved for use in both episodic and chronic migraine patient populations in the USA. Additionally, both galcanezumab and erenumab were also approved in both these patients populations in the EU in 2018. Fremanezumab was approved for episodic and chronic migraine in the EU in 2019. Although the focus of the Editorial was not on the specific geographies and patient populations for whom these medications are approved, the omitted information results in an unbalanced statement that could be unintentionally misleading and result in further restrictions or delays in access to these new therapies in regions other than the UK. We believe that patients should have access to as many treatment options as possible to optimise the likelihood of a positive response to treatment.

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- 1 The Lancet Neurology. Complicated decisions on new migraine-prevention therapies. *Lancet Neurol* 2019; **18**: 221.

Early carotid surgery versus stenting in younger patients

The recently published individual patient meta-analysis by the Carotid

Stenosis Trialists' Collaboration,¹ which pools the findings of the four largest randomised controlled trials comparing carotid endarterectomy (CEA) with carotid artery stenting (CAS), provides valuable new data concerning periprocedural and (particularly) late outcomes of CEA and CAS in patients with symptomatic stenosis. Aside from clearly showing that, once the periprocedural period has elapsed, CAS was as durable as CEA, the meta-analysis also confirmed that the magnitude of the periprocedural risk (death or stroke within 0–30 days after the procedure) ultimately determines which treatment modality is safer and therefore preferable in individual patients in the long-term.

The collaboration identified several subgroups of patients in which 30-day rates of death and stroke after CAS were similar to those after CEA. One such subgroup was that of patients younger than 65 years. However, we were not informed if this similarity remained valid when 30-day rates of death and stroke were stratified for delays between symptom onset and surgery. The European Society for Vascular Surgery guidelines on the management of carotid artery disease (in line with virtually all other contemporary guidelines) recommend that carotid interventions should be done as soon as possible after the onset of symptoms, preferably within 7–14 days.² Such rapid intervention is recommended because the highest risk of recurrent stroke is during this initial time period, and this period is when CEA is at its most effective.³

However, in an earlier meta-analysis of the same four randomised controlled trials by the Carotid Stenosis Trialists Collaboration, CAS was associated with a significantly higher proportion of periprocedural strokes and deaths (24/287 [8%]), compared with CEA (3/226 [1%]), when performed within 7 days of symptom onset (risk ratio 6.7, 95% CI 2.1–21.9).⁴ The authors stated that this risk was calculated after adjustment for age at treatment,

sex, and type of qualifying event (transient ischaemic attack, stroke, or amaurosis fugax).⁴ As a consequence, the Carotid Guidelines Writing Group of the European Society for Vascular Surgery advised that "Patients who are to undergo revascularisation within the first 14 days after onset of symptoms should undergo [CEA], rather than [CAS]."² To avoid any future confusion, the Carotid Stenosis Trialists Collaboration should clarify whether patients younger than 65 years who underwent CAS within 7–14 days of symptom onset had a 30-day rate of death or stroke similar to that observed after CEA.

I declare no competing interests.

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- 1 Brott TG, Calvet D, Howard G, et al. Long-term outcomes of stenting and endarterectomy for symptomatic carotid stenosis: a preplanned pooled analysis of individual patient data. *Lancet Neurol* 2019; **18**: 348–56.
- 2 Naylor AR, Ricco JB, de Borst GJ, et al. Management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018; **55**: 3–86.
- 3 Naylor AR. Time is brain: an update. *Expert Rev Cardiovasc Ther* 2015; **13**: 1111–26.
- 4 Rantner B, Kollertis B, Roubin GS, et al. Early endarterectomy carries a lower procedural risk than early stenting in patients with symptomatic stenosis of the internal carotid artery: results from 4 randomized controlled trials. *Stroke* 2017; **48**: 1580–87.

Authors' reply

We thank A Ross Naylor for his letter regarding our pooled analysis of long-term outcomes in four randomised clinical trials comparing carotid endarterectomy (CEA) with carotid artery stenting (CAS) as treatments for symptomatic carotid stenosis. In our Article,¹ we reported that the subgroup of patients younger than 65 years had similar rates of stroke or death at 30 days after treatment, with a hazard ratio (HR) for CAS versus CEA of 0.83 (95% CI 0.56–1.21). Naylor states that "the Carotid Stenosis Trialists

Collaboration should clarify whether patients younger than 65 years who underwent CAS within 7–14 days of symptom onset had a 30-day rate of death or stroke similar to that observed after CEA.” We have now done this subgroup analysis, but even in the pooled analysis of 4754 patients, only 367 patients met both of the restrictions on age (<65 years) and time from symptoms to intervention (≤ 14 days). Of the 173 patients who had CEA, three (2%) had a stroke or died within 30 days of treatment, compared with six (3%) of the 194 patients who had CAS ($p=0.51$; per-protocol analysis). The HR for CAS versus CEA was 1.79 (95% CI 0.45–7.15; $p=0.42$). For the intention-to-treat analysis (over the 120-day period after randomisation), 11 (6%) of the 173 patients who had CEA had a stroke or died, compared with ten (5%) of the 194 patients who had CAS ($p=0.66$). The HR was 0.79 (95% CI 0.34–1.87; $p=0.59$).

Thus, we have found no evidence of a difference between the risks of CEA and

CAS in younger patients treated within 14 days of symptom onset; however, the high p values and wide CIs reflect the low number of events in these small groups. Therefore, we cannot conclude that CEA is safer than CAS when done less than 14 days after symptom onset, nor can we exclude true differences. The analysis of the pooled data quoted by Naylor, suggesting that early CEA was safer than early CAS, was a non-randomised comparison,² and the decision to operate on patients early was probably made on different grounds to the decision to do early CAS. The proportion of patients treated early were also quite different in the four trials. On the contrary, in our earlier pooled analysis of the same trials,³ data showing that CAS has similar risks to CEA in patients younger than 65 years are more robust, in part because randomisation ensured that the younger patients were matched in both treatment groups. Therefore, the data do not support recommending CEA rather than CAS in patients

younger than 65 years within the first 14 days of symptom onset.

We declare no competing interests

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- 1 Brott TG, Calvert D, Howard G, et al. Long-term outcomes of stenting and endarterectomy for symptomatic carotid stenosis: a preplanned pooled analysis of individual patient data. *Lancet Neurol* 2019; **18**: 348–56.
- 2 Rantner B, Kollertis B, Roubin GS, et al. Early endarterectomy carries a lower procedural risk than early stenting in patients with symptomatic stenosis of the internal carotid artery: results from 4 randomized controlled trials. *Stroke* 2017; **48**: 1580–87.
- 3 Howard G, Roubin GS, Jansen O, et al. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from four randomised trials. *Lancet* 2016; **387**: 1305–11.