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**To cite:** Collette SL, Rodgers MP, van Walderveen MAA, *et al.* Management of extracranial carotid artery stenosis during endovascular treatment for acute ischaemic stroke: results from the MR CLEAN Registry. *Stroke & Vascular Neurology* 2023;**8**: e001891. doi:10.1136/svn-2022-001891

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/svn-2022-001891>).

Received 26 July 2022  
Accepted 2 November 2022  
Published Online First  
26 December 2022



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## ABSTRACT

**Background** The optimal management of ipsilateral extracranial internal carotid artery (ICA) stenosis during endovascular treatment (EVT) is unclear. We compared the outcomes of two different strategies: EVT with vs without carotid artery stenting (CAS).

**Methods** In this observational study, we included patients who had an acute ischaemic stroke undergoing EVT and a concomitant ipsilateral extracranial ICA stenosis of  $\geq 50\%$  or occlusion of presumed atherosclerotic origin, from the Dutch Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry (2014–2017). The primary endpoint was a good functional outcome at 90 days, defined as a modified Rankin Scale score  $\leq 2$ . Secondary endpoints were successful intracranial reperfusion, new clot in a different vascular territory, symptomatic intracranial haemorrhage, recurrent ischaemic stroke and any serious adverse event.

**Results** Of the 433 included patients, 169 (39%) underwent EVT with CAS. In 123/168 (73%) patients, CAS was performed before intracranial thrombectomy. In 42/224 (19%) patients who underwent EVT without CAS, a deferred carotid endarterectomy or CAS was performed. EVT with and without CAS were associated with similar proportions of good functional outcome (47% vs 42%, respectively; adjusted OR (aOR), 0.90; 95% CI, 0.50 to 1.62). There were no major differences between the groups in any of the secondary endpoints, except for the increased odds of a new clot in a different vascular territory in the EVT with CAS group (aOR, 2.96; 95% CI, 1.07 to 8.21).

**Conclusions** Functional outcomes were comparable after EVT with and without CAS. CAS during EVT might be a feasible option to treat the extracranial ICA stenosis but randomised studies are warranted to prove non-inferiority or superiority.

## INTRODUCTION

In general, 10–20% of the patients with an acute ischaemic stroke due to a proximal intracranial occlusion of the anterior circulation have a concomitant stenosis  $\geq 50\%$  or occlusion of the ipsilateral extracranial

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The optimal management of concomitant ipsilateral extracranial internal carotid artery (ICA) stenosis during endovascular treatment (EVT) is unclear.

## WHAT THIS STUDY ADDS

⇒ In this non-randomised, observational study from the MR CLEAN Registry, the outcome of carotid artery stenting (CAS) performed during EVT was comparable to EVT without CAS.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ CAS during EVT might be a feasible option to treat the concomitant ipsilateral extracranial ICA stenosis but randomised studies are warranted to prove non-inferiority or superiority.

internal carotid artery (ICA).<sup>1 2</sup> These concomitant ipsilateral ICA stenosis are associated with poor functional outcome after intravenous thrombolysis and may complicate endovascular treatment (EVT).<sup>3</sup> Although EVT has become standard of care in patients with an acute ischaemic stroke due to large vessel occlusion, the optimal treatment approach of a concomitant ipsilateral ICA stenosis remains unclear.<sup>4–12</sup> Some interventionists prefer to perform EVT with carotid artery stenting (CAS), while others advocate a more conservative approach without CAS, but with percutaneous transluminal angioplasty (PTA) to gain intracranial access, if necessary. In the latter case, carotid endarterectomy or CAS are usually considered as a deferred treatment if a patient shows adequate neurological improvement and residual high-grade ICA stenosis is still present.<sup>13</sup>

EVT with CAS might reduce the risk of a recurrent embolic stroke due to new

thrombus formation and intracranial embolisation.<sup>6</sup> However, it could increase the chance of a cerebral hyperperfusion syndrome with subsequent intracranial haemorrhage.<sup>14 15</sup> Also, with concomitant dual antiplatelet therapy to prevent in-stent thrombosis, the risk of an intracranial bleeding may increase.<sup>16</sup> It is unclear if these risks outweigh the potential complications of a deferred treatment.<sup>4-6 16-18</sup>

In patients where CAS is performed during EVT, it can be done before or directly after thrombectomy. It is postulated that the CAS first approach leads to an immediately improved intracranial collateral circulation, and consequently increased perfusion during and after EVT.<sup>11</sup> However, the thrombectomy first approach may lead to faster intracranial recanalisation and subsequent improved outcome.<sup>12</sup>

We compared clinical, technical and safety endpoints of EVT with CAS vs EVT without CAS in patients with a concomitant ipsilateral extracranial ICA stenosis in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry.

## METHODS

### Study design

This was a non-randomised, observational study of prospectively collected data from the MR CLEAN Registry (online supplemental appendix). The MR CLEAN Registry is a multicentre, observational study in which all patients who were treated endovascularly for acute ischaemic stroke in the Netherlands were enrolled from March 2014 to November 2017. The study design and patient eligibility criteria have been reported previously.<sup>19</sup>

### Participants

Patients with an acute ischaemic stroke due to a proximal intracranial occlusion of the anterior circulation who underwent EVT (defined as an intracranial treatment by mechanical thrombectomy or administration of local intra-arterial thrombolytics), and who had a concomitant ipsilateral extracranial ICA stenosis of  $\geq 50\%$  or occlusion of presumed atherosclerotic origin, were included. A stenosis or occlusion was assumed to be of atherosclerotic origin if other aetiologies (dissection, floating thrombus, carotid web and pseudo-occlusion) could be excluded. Exclusion criteria were age under 18 years, EVT in a non-MR CLEAN centre, initiation of EVT more than 6.5 hours after onset of symptoms, presence of an ICA dissection, presence of a pseudo-occlusion and a pre-stroke modified Rankin Scale (mRS) score  $> 2$ . Dissection was defined as a narrowing of the ICA above the level of the carotid bifurcation with distal tapering of the ICA, with or without a distal occlusion in the ICA segment. Presence of a dissection was assessed on baseline single-phase CT angiography (CTA) and/or digital subtraction angiography (DSA) by a core laboratory. Suspected pseudo-occlusion was defined as filling of the carotid bifurcation

of the ICA with contrast and a gradual antegrade contrast fading in the ICA, leading to intracranial occlusion. Presence of a pseudo-occlusion was assessed on single-phase CTA by a core laboratory.<sup>20</sup>

### Endovascular treatment

Endovascular treatment consisted of arterial catheterisation with a microcatheter to the level of the intracranial occlusion, followed by mechanical thrombectomy, thrombus aspiration or both, with or without administration of a thrombolytic agent. The method of endovascular treatment, the choice for EVT with CAS and the decision on the type of stent was left to the discretion of the interventionist. There was no uniform protocol on antiplatelet regimen during and after CAS, and data on the periprocedural antiplatelet regimen used were not systematically recorded in the MR CLEAN Registry.<sup>19</sup>

### Data collection

A core laboratory, blinded to the clinical characteristics and outcome, evaluated imaging data on location of the intracranial occlusion, occlusion side, collateral score, presence, location and type of a concomitant ipsilateral ICA lesion (including ICA stenosis  $\geq 50\%$ , occlusion, dissection, floating thrombus, carotid web and pseudo-occlusion), EVT with CAS, EVT with PTA, time from onset to recanalisation, extended Thrombolysis In Cerebral Infarction (eTICI) score before and after EVT, occurrence of a new clot in a different vascular territory and presence of symptomatic intracranial haemorrhage (sICH) within 90 days after EVT.

The presence and type of a concomitant ipsilateral ICA stenosis was based on core laboratory assessment of the baseline CTA. In case of missing CTA data, a core laboratory evaluation of the concomitant ipsilateral ICA stenosis on DSA was used. The core laboratory only assessed whether an ICA stenosis  $\geq 50\%$  or occlusion was present, and therefore a distinction in the exact degree of the stenosis could not be made. Additional re-assessment of DSA images was performed for the EVT with CAS group by two neuro-interventionists (MU and RB) to acquire data on the thrombectomy first approach and CAS first approach.

Data on possible deferred treatment of patients who underwent EVT without CAS were obtained from comprehensive or peripheral stroke centres. When no deferred surgical or endovascular revascularisation was performed, the reasons for withholding treatment were recorded.

The applied EVT technique (ie, whether the thrombectomy attempt was with stent retriever, aspiration, intra-arterial thrombolytics or a combination of techniques) during the first thrombectomy attempt was unknown for a relatively high number of patients in the EVT with CAS group. We therefore also aimed to complete these data during the re-assessment of the DSA images.

Collateral filling was assessed on baseline single-phase CTA imaging using a categorical scale: a collateral score of 0 indicated absent collaterals, a score of 1 indicated

collateral filling >0% but ≤50% of the occluded middle cerebral artery territory, a score of 2 indicated collateral filling >50% but <100% and a score of 3 indicated 100% collateral filling.<sup>21</sup>

### Endpoints

The primary endpoint was a good functional outcome, defined as an mRS score of ≤2 at 90 days after EVT. The mRS is a categorical scale (0, no symptoms; 6, death) that reflects the degree of disability after a stroke. A score of 2 or lower reflects independency for activities of daily living.<sup>22</sup>

The secondary technical endpoint was successful intracranial reperfusion immediately after EVT, which was defined as an eTICI score of ≥2B. The eTICI is a categorical scale (range 0–3; the higher the number, the greater the degree of reperfusion) that reflects the degree of reperfusion, and is scored on DSA imaging.<sup>23</sup> If the frontal or lateral DSA run immediately after EVT was unavailable, an eTICI score of 2A was the highest possible grading.<sup>19</sup> Safety endpoints were occurrence of a new clot in a different vascular territory, occurrence of sICH within 90 days after EVT, recurrent ischaemic stroke within 90 days after EVT and occurrence of any serious adverse event within 90 days after EVT. A new clot in a different vascular territory was defined as a remaining proximal intracranial occlusion on last DSA run that did not match the thrombus locations scored on baseline CTA, and had changed either from one territory to another or from a distal occlusion location to a more proximal location. Whether this endpoint could be assessed in the absence of a frontal or lateral DSA run immediately after EVT, was left to the discretion of the core laboratory assessor.<sup>19</sup> An intracranial haemorrhage was considered to be symptomatic if patients died or deteriorated neurologically (a decline of at least 4 points on the National Institutes of Health Stroke Scale (NIHSS)) and the haemorrhage was related to the clinical deterioration (according to the Heidelberg criteria).<sup>24</sup> Recurrent ischaemic stroke was defined as a new ischaemic stroke that was confirmed on imaging, led to corresponding neurological deficits or resulted in death. Any serious adverse event was defined as any untoward medical occurrence or effect causing mortality, a life-threatening situation, prolonged hospitalisation or persistent significant disability.<sup>19</sup>

The primary and secondary endpoints were compared between patients who underwent EVT with and without CAS. The choice for these groups was based on the treatment decision to be made in the acute phase. To avoid selection bias, the control group not only consisted of patients who had undergone deferred treatment but also of patients who were not treated in the deferred phase (one of the requirements of a deferred treatment is that the patient should have a non-disabling stroke, which increases the chance of a good functional outcome at 90 days. Moreover, during EVT it is difficult to reliably predict which patients will or will not recover).

### Statistical analysis

Baseline characteristics, procedural characteristics and observed outcomes were presented for the EVT with and without CAS groups.

To facilitate statistical comparison despite the small number of observations in some of the categories, the mRS score and eTICI score were dichotomised into good and poor functional outcome, and successful and unsuccessful intracranial reperfusion, respectively.

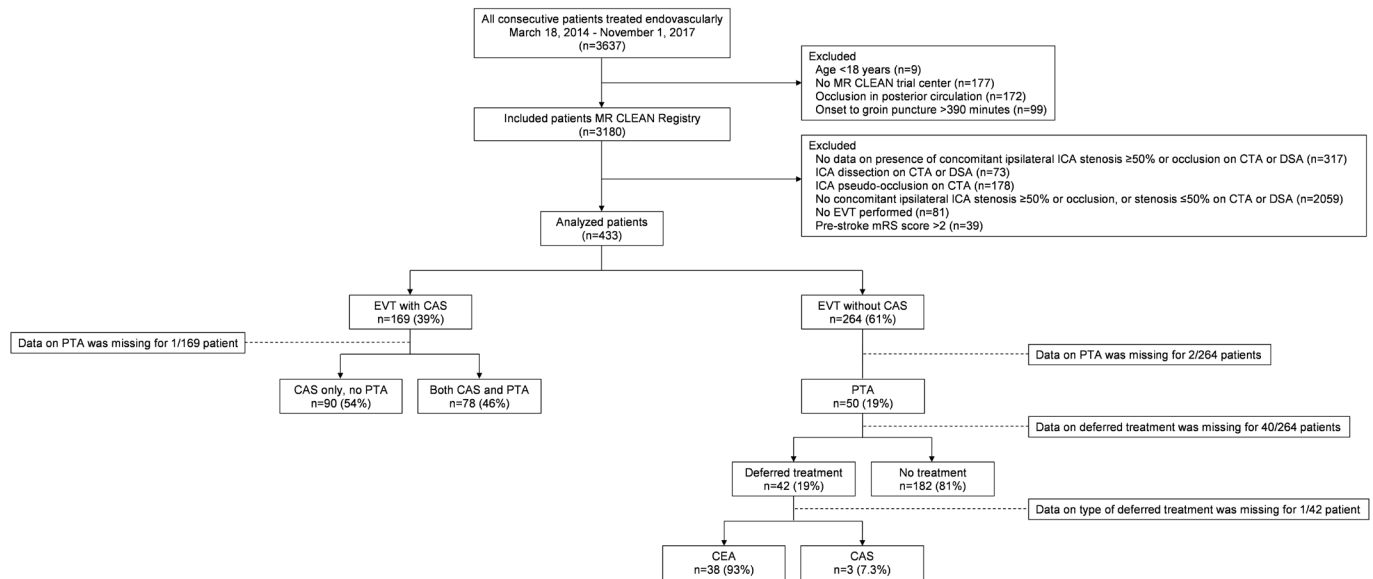
Both univariable and multivariable logistic regression analyses were performed to analyse the association between EVT with CAS and the dichotomous primary and secondary endpoints. For all endpoints, a sensitivity analysis was conducted in which patients who were not treated with intravenous thrombolysis were excluded. An additional subgroup analysis was performed within the group of patients treated with CAS during EVT to determine the association between the CAS first approach and good functional outcome at 90 days. Results were displayed as (adjusted) OR ((a)OR) with 95% CI. In the multivariable analyses, results were adjusted for age, sex, a medical history of atrial fibrillation, hypercholesterolaemia and myocardial infarction, smoking, antiplatelet use, coumarin use, NIHSS score at baseline, Alberta Stroke Programme Early CT Score, collateral score, intravenous thrombolysis, time from onset to recanalisation and PTA during EVT. In the subgroup analysis, we only adjusted for age, sex, NIHSS score at baseline and collateral score due to the limited sample size. The choice of the covariables was based on generally known associations related to stroke and/or cardiovascular outcomes, and on significant differences that we found between the EVT with and without CAS groups. Covariables were included in the multivariable analyses if they increased or decreased the unadjusted OR with ≥10%. The covariables that did not change the OR with ≥10%, but were considered relevant because of previous publications, were still included.<sup>25</sup>

Missing data were imputed using multiple imputation by chained equations based on relevant covariables and outcome. Two-sided p values, or one-sided p values in case of a  $\chi^2$  test, of <0.05 were considered statistically significant. Data were analysed using SPSS Statistics V.23.0 (IBM Corp, Armonk, New Y).

## RESULTS

### Data selection

Between March 2014 and November 2017, 3637 patients with acute ischaemic stroke received EVT of whom 3180 patients were included in the analysis of MR CLEAN Registry. The inclusion and exclusion criteria of our study were met by 433 of the 3180 patients. EVT with CAS was performed in 169 of the 433 (39%) included patients. Follow-up data of 40 of the 264 patients who underwent EVT without



**Figure 1** Flowchart of included patients. CAS, carotid artery stenting; CEA, carotid endarterectomy; CTA, CT angiography; DSA, digital subtraction angiography; EVT, endovascular treatment; ICA, internal carotid artery; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Score; PTA, percutaneous transluminal angioplasty.

immediate CAS were missing. Of the remaining 224 patients who had no CAS during EVT, 42 of the 224 (19%) underwent a deferred treatment by carotid endarterectomy or CAS and 182 of the 224 (81%) had no deferred treatment (figure 1).

### Baseline characteristics

Patients who underwent EVT with CAS were younger, had a lower prevalence of atrial fibrillation or myocardial infarction, had a higher prevalence of hypercholesterolaemia, were less likely to use coumarins, had a more favourable collateral filling and were more likely to receive intravenous thrombolysis compared with patients who underwent EVT without CAS (table 1).

### Procedural characteristics

For patients who underwent EVT with and without CAS, procedural characteristics were essentially equal, with the exception of PTA (46% vs 19%, respectively,  $p<0.001$ ). A procedural stent occlusion occurred in 7/111 (6.3%) patients (table 2).

In the EVT with CAS group, 123/168 (73%) patients received CAS before intracranial thrombectomy. Time from stroke onset to recanalisation was comparable between the CAS and thrombectomy first approaches (median time, 272 min (IQR, 213–328) and 253 min (IQR, 208–343), respectively,  $p=0.75$ ).

In the EVT without CAS group, 182/224 (81%) patients did not receive a deferred treatment. Reasons for withholding carotid endarterectomy or CAS were the absence of an ICA stenosis  $\geq 50\%$  during follow-up ( $n=45/141$ , 32%), an ICA occlusion ( $n=25/141$ , 18%) or a poor functional status ( $n=71/141$ , 50%).

## Outcome

### Primary endpoint

The proportion of patients with a good functional outcome was comparable between EVT with and without CAS groups (47% vs 42%, respectively; OR, 1.32; 95% CI, 0.88 to 1.98, figure 2). After adjustment for possible confounders, the odds of good functional outcome was still similar between the EVT with and without CAS groups (aOR, 0.90; 95% CI, 0.50 to 1.62) (online supplemental table S1). Exclusion of those patients treated without intravenous thrombolysis did not change the direction of the results (online supplemental table S2).

### Secondary endpoints

Between patients who underwent EVT with and without CAS, no significant differences were found in the rate of successful intracranial reperfusion (62% vs 64%, respectively), new clot in different vascular territory (9.1% vs 5.4%, respectively), sICH (4.7% vs 7.6%, respectively), recurrent ischaemic stroke (1.8% vs 0.8%) and any serious adverse event (43% vs 38%, respectively) (table 3). In the group of patients who received a deferred treatment, 1/42 (2.4%) patient, who was treated with carotid endarterectomy, developed a recurrent ischaemic stroke. In 60/420 (14%) patients, the intracranial reperfusion status was scored with a maximum eTICI score of 2A due to unavailability of a final frontal or lateral DSA run. The proportion of patients with a missing final two-directional DSA run was comparable between the EVT with and without CAS groups (26/165 (16%) vs 34/255 (13%);  $p=0.49$ ). After adjustments, EVT

**Table 1** Baseline characteristics of EVT with and without CAS patients

Characteristics	EVT with CAS (n=169)	EVT without CAS (n=264)	P value
Age - years	70 (63–77)	72 (64–79)	0.04
Male	120/169 (71)	166/264 (63)	0.08
Medical history			
Atrial fibrillation	11/168 (6.5)	45/261 (17.2)	<0.01
Diabetes mellitus	22/167 (13.2)	40/260 (15.4)	0.53
Hypercholesterolaemia	64/167 (38.3)	71/249 (28.5)	0.04
Hypertension	83/166 (50.0)	139/259 (53.7)	0.46
Myocardial infarction	12/166 (7.2)	44/260 (16.9)	<0.01
Peripheral artery disease	25/167 (15.0)	32/261 (12.3)	0.42
Previous stroke	20/168 (11.9)	38/261 (14.6)	0.43
Current smoker	65/140 (46.4)	69/190 (36.3)	0.06
Current medication use			
Antiplatelet	44/166 (26.5)	81/260 (31.2)	0.30
DOAC	2/168 (1.2)	4/259 (1.5)	>0.99
Coumarin	8/168 (4.8)	34/262 (13.0)	0.01
Heparin	0/167 (0)	6/259 (2.3)	0.09
Antihypertensive medication	81/166 (48.8)	145/256 (56.6)	0.11
Statin	58/165 (35.2)	94/258 (36.4)	0.79
Pre-stroke mRS score >0	28/165 (17.0)	56/255 (22.0)	0.21
Left hemisphere	86/169 (50.9)	145/264 (54.9)	0.41
Ipsilateral extracranial ICA lesion			
Carotid stenosis 50–99%	68/169 (40.2)	130/264 (49.2)	0.07
Carotid occlusion	101/169 (59.8)	134/264 (50.8)	0.07
NIHSS score	16 (11–19)	16 (12–19)	0.68
ASPECTS	8 (7–10)	9 (7–10)	0.87
Collateral filling			
Absent collaterals	3/161 (1.9)	22/255 (8.6)	
<50% of occluded territory	48/161 (29.8)	99/255 (38.8)	
50–99% of occluded territory	73/161 (45.3)	94/255 (36.9)	
100% of occluded territory	37/161 (23.0)	40/255 (15.7)	
Intravenous thrombolysis	150/168 (89.3)	214/262 (81.7)	0.03
Pre-intervention DBP - mm Hg	82±16	83±15	0.92
Pre-intervention SBP - mm Hg	154±26	154±23	>0.99

Data are presented as n (%), mean±SD or median (IQR). The data in this table are based on the data set before imputation. For some variables, the denominators are smaller than the number of patients included due to missing data. ASPECTS, Alberta Stroke Programme Early CT Score; CAS, carotid artery stenting; DBP, diastolic blood pressure; DOAC, direct oral anticoagulants; EVT, endovascular treatment; ICA, internal carotid artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke; SBP, systolic blood pressure.

with CAS was associated with the occurrence of a new clot in a different vascular territory (aOR, 2.96; 95% CI, 1.07 to 8.21). The risk of successful intracranial reperfusion, sICH, and any serious adverse event were comparable between the EVT with and without CAS groups. For recurrent ischaemic stroke, the aOR could not be reliably determined due to the limited number of observations (table 3; online supplemental tables S3–7). The directions of the results did

not change after exclusion of those patients treated without intravenous thrombolysis (online supplemental table S2).

Within the EVT with CAS group, the proportion of good functional outcome was essentially equal for the CAS first approach and thrombectomy first approach (48% vs 48%; OR, 1.05; 95% CI, 0.52 to 2.12 and aOR, 1.03; 95% CI, 0.48 to 2.22) (online supplemental table S8).

**Table 2** Procedural characteristics of EVT with and without CAS patients

Characteristics	EVT with CAS (n=169)	EVT without CAS (n=264)	P value
EVT technique, first attempt			0.07
Stent retriever	80/169 (47.3)	174/264 (65.9)	
Aspiration	52/169 (30.8)	69/264 (26.1)	
Intra-arterial thrombolytics	0/169 (0)	1/264 (0.4)	
Unknown	37/169 (21.9)	20/264 (7.6)	
EVT technique, second attempt			0.28
Stent retriever	16/43 (37.2)	26/61 (42.6)	
Aspiration	20/43 (46.5)	31/61 (50.8)	
Intra-arterial thrombolytics	7/43 (16.3)	4/61 (6.6)	
PTA performed	78/168 (46.4)	50/262 (19.1)	<0.001
Stenting before EVT	123/168 (73.2)	N/A	
Procedural stent occlusion	7/111 (6.3)	N/A	
Time from onset to arterial puncture - min	190 (141–242)	195 (155–245)	0.55
Time from onset to recanalisation - min	268 (212–330)	260 (213–315)	0.42

Data are presented as n (%) or median (IQR). The data in this table are based on the data set before imputation. For some variables, the denominators are smaller than the number of patients included due to missing data.

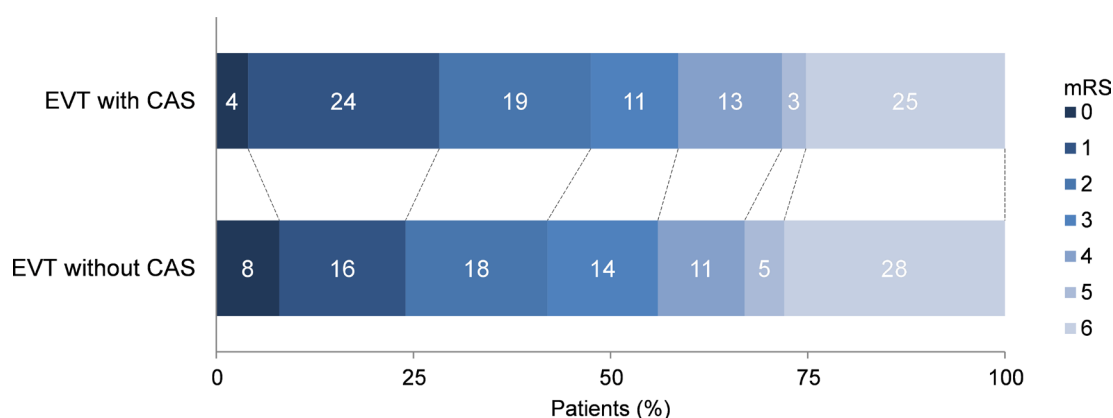
CAS, carotid artery stenting; EVT, endovascular treatment; N/A, not applicable; PTA, percutaneous transluminal angioplasty.

## DISCUSSION

Clinical, technical and safety outcomes were comparable for EVT with and without CAS in this large, non-randomised, observational, multicentre study among patients who had an acute ischaemic stroke with a concomitant ipsilateral extracranial ICA stenosis of presumed atherosclerotic origin. In addition, the odds of good functional outcome was essentially equal for the CAS first and thrombectomy first approach.

Several studies showed discrepant results regarding the effect of EVT with CAS on functional outcome at 90 days. In a retrospective, observational study of the Thrombectomy in Tandem Lesions (TITAN) Registry, the rate of good functional outcome was found to be higher in patients who underwent EVT with CAS (58%) than in patients who underwent EVT without CAS (42%). After adjustment for confounders, an association between EVT

with CAS and good functional outcome did however no longer exist. Compared with our study, a stronger association could have been expected between EVT with CAS and functional outcome in the TITAN Registry due to the stricter criteria used to define an ipsilateral extracranial ICA stenosis ( $\geq 50\%$  vs  $\geq 90\%$ ). This was however not reflected in the adjusted results, possibly because, as in our study, a proportion of patients in the EVT without CAS group underwent deferred treatment.<sup>6</sup> In a pooled analysis of the Endovascular Treatment in Ischemic Stroke (ETIS) and TITAN registries,<sup>26</sup> and in the Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke (STRATIS) Registry,<sup>4</sup> good functional outcome was observed more frequently in patients who underwent EVT with CAS than in patients who underwent EVT without CAS (57% vs 45% and 68% vs 42%, respectively). In these studies,



**Figure 2** Functional outcome at 90 days of EVT with and without CAS patients. The data in this figure are based on the data set before imputation. CAS, carotid artery stenting; EVT, endovascular treatment; mRS, modified Rankin Scale.

**Table 3** Secondary endpoints in EVT with and without CAS patients

Endpoint	EVT with CAS (n=169)	EVT without CAS (n=264)	OR	95% CI	aOR*	95% CI
Successful intracranial reperfusion†	101/164 (61.6)	164/256 (64.1)	0.91	0.60 to 1.36	0.73	0.43 to 1.23
New clot in different vascular territory‡	14/154 (9.1)	13/241 (5.4)	1.81	0.84 to 3.92	2.96	1.07 to 8.21
Symptomatic intracranial haemorrhage§	8/169 (4.7)	20/264 (7.6)	0.61	0.26 to 1.41	0.73	0.23 to 2.37
Recurrent ischaemic stroke¶	3/169 (1.8)	2/264 (0.8)	2.37	0.39 to 14.32	**	
Any serious adverse event††	72/169 (42.6)	99/264 (37.5)	1.24	0.83 to 1.83	1.27	0.76 to 2.11

Data are presented as n (%). The data in this table are partly based on the data set before imputation (number of patients). For some variables, the denominators are smaller than the number of patients included due to missing data.

\*Results were adjusted for age, sex, a medical history of atrial fibrillation, hypercholesterolaemia and myocardial infarction, smoking, antiplatelet use, coumarin use, National Institutes of Health Stroke Scale score at baseline, Alberta Stroke Programme Early CT Score, collateral score, intravenous thrombolysis, time from onset to recanalisation and percutaneous transluminal angioplasty during endovascular treatment.

†Successful intracranial reperfusion was defined as extended Thrombolysis In Cerebral Infarction score of  $\geq 2B$ .

‡New clot in a different vascular territory was defined as a remaining proximal intracranial occlusion on last digital subtraction angiography run that did not match the thrombus locations scored on baseline CT angiography, and had changed either from one territory to another or from a distal occlusion location to a more proximal location.

§An intracranial haemorrhage was considered to be symptomatic if patients died or deteriorated neurologically (a decline of at least 4 points on the National Institutes of Health Stroke Scale) and the haemorrhage was related to the clinical deterioration (according to the Heidelberg criteria).

¶Recurrent ischaemic stroke was defined as a new ischaemic stroke that was confirmed on imaging, led to corresponding neurological deficits or resulted in death.

\*\*The aOR could not be reliably determined due to the limited number of observations of recurrent ischaemic stroke.

††Any serious adverse event was defined as any untoward medical occurrence or effect causing mortality, a life-threatening situation, prolonged hospitalisation or persistent significant disability.

(a)OR, (adjusted) OR; CAS, carotid artery stenting; EVT, endovascular treatment.

the association between EVT with CAS and good functional outcome remained in the multivariable analyses.<sup>4,26</sup> The analyses of the TITAN<sup>6</sup> and STRATIS<sup>4</sup> registries were included in a systematic review and meta-analysis,<sup>5</sup> in which an association between EVT with CAS and a more favourable outcome at 90 days was found. No definite recommendation on the treatment of concomitant ipsilateral ICA stenosis could however be given, as the review mainly consisted of observational studies due to the lack of randomised controlled trials.<sup>5</sup> Thus, to overcome issues such as confounding and selection bias, a randomised controlled trial seems warranted. A randomised pilot study has already shown the feasibility of this next step.<sup>10</sup>

Unlike previous reported studies, we focused on the patients who underwent EVT without immediate CAS. Only 19% of the patients within this group received a deferred treatment by means of a carotid endarterectomy or CAS. The most common reason for withholding carotid endarterectomy or CAS was a poor functional status. This may suggest that some patients underwent EVT with CAS who would not have qualified for carotid endarterectomy or CAS in case of a deferred treatment. Other important reasons to withhold deferred treatment were an ICA stenosis  $<50\%$  or complete occlusion during follow-up imaging. Two causes may account for these differences between baseline and follow-up. First, baseline assessments between the interventionist and core laboratory may have varied due to the different imaging modalities that were used to diagnose a stenosis or occlusion (baseline CTA vs DSA) and due to inter-rater variability.

Second, the degree of the stenosis may have reduced to a stenosis  $<50\%$  due to the effect of PTA only. These patients may benefit from a prolonged follow-up, as the ICA stenosis or occlusion was not treated more definitely.

Contrary to our findings, EVT with CAS was associated with successful intracranial reperfusion in the pooled analysis of the ETIS and TITAN registries.<sup>26</sup> A possible explanation for this discrepancy is that in the MR CLEAN Registry, an eTICI score of 2A was the highest possible grading if the frontal or lateral DSA run immediately after EVT was unavailable.<sup>19</sup> Although the distribution of patients with a missing final two-directional DSA run seemed comparable between the EVT with and without CAS groups, we did find a numerical difference at the expense of the EVT with CAS group. The rate of patients with successful intracranial reperfusion might therefore have been underestimated in the EVT with CAS group, however, we doubt that this had a significant impact. Another explanation for these discrepant results might be new embolisation due to stent-related thrombosis. Although EVT with CAS could prevent recurrent embolisation from the concomitant ipsilateral ICA stenosis and consequently poor reperfusion rates, one of its complications is in-stent thrombosis. As in-stent thrombosis might also increase the risk of new intracranial embolisation, an association between EVT with CAS and successful intracranial reperfusion might disappear. The incidence of in-stent thrombosis was not mentioned in previous studies and could therefore not be compared with the incidence found in our study.

No major safety concerns were observed after EVT with CAS, despite an association with the occurrence of a new clot in a different vascular territory. A reliable conclusion regarding this possible complication could not be drawn due to the small number of observations. More importantly, this increased risk did not translate into a lower chance of good functional outcome. Furthermore, the rate of sICH was not found to be higher in the EVT with CAS patients, even though a substantial part (89%) received intravenous thrombolysis before EVT. This is important, because increased bleeding risks are a feared complication of EVT with CAS. Our findings on risk of sICH are in line with other studies.<sup>4–6 18</sup>

This study has limitations. First, owing to the retrospective study design, no selection criteria for EVT with CAS and no standardised intervention techniques were maintained. Despite our best efforts to adjust for confounders, treatment preference, personal experience and patient selection of the interventionists may have influenced our results. Second, no data were available on antiplatelet regimes after EVT with CAS. Therefore, influence of treatment characteristics such as type, dosage and number of antiplatelet agents, as well as duration of therapy on functional outcome could not be determined. Third, we could not analyse the effect of stenosis characteristics (such as the exact stenosis grade and the stenosis composition) on patient outcomes and treatment decisions. Patients with an ipsilateral carotid stenosis of 50–70% may have diluted the treatment effect of CAS during EVT. Therefore, future clinical trials among patients with a stenosis grade  $\geq 50\%$  should be sufficiently powered to stratify the data by stenosis grade (50–70%, 70–90% and 90–99% or complete occlusion). An alternative would be to include only patients with a stenosis grade of 70–90%. This approach would however hamper a direct comparison with other grades (50–70%, 90–99% or complete occlusion), and in the current guidelines the threshold for treatment with deferred elective carotid endarterectomy or CAS starts at a stenosis grade  $\geq 50\%$ .<sup>27 28</sup> Fourth, the underlying reasons for CAS and PTA during EVT (eg, to gain access to remove the distal intracranial occlusion) were unknown. Fifth, the study lacked periprocedural carotid endarterectomy/CAS data and detailed follow-up data of the patients who had undergone deferred treatment. This may have hampered further understanding of the results. Finally, 6.2% of the patients were lost to follow-up for unknown reasons. This may have biased our results in unpredictable ways, although the rate of drop-outs was comparable for the EVT with and without CAS groups.

To conclude, in our non-randomised analysis, clinical, technical and safety endpoints were comparable for EVT with and without CAS in patients who had an acute ischaemic stroke with a concomitant ipsilateral extracranial ICA stenosis of presumed atherosclerotic origin. Optimal management of a concomitant ipsilateral extracranial ICA stenosis in patients who had an acute ischaemic stroke remains however uncertain. Phase 3 randomised trials are

urgently warranted to prove non-inferiority or superiority of CAS during EVT, taking the degree of carotid artery stenosis into account.

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**Acknowledgements** We would like to thank the MR CLEAN Registry Investigators—group authors (online supplemental appendix)

**Contributors** SLC, MPR, RPHB and MU contributed to the study conception and design. Data acquisition, analysis or interpretation were performed by all authors. The first draft of the manuscript was written by SLC, MPR, RPHB and MU and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Guarantor: SLC.

**Funding** The MR CLEAN Registry was partly funded by Toegepast Wetenschappelijk Instituut voor Neuromodulatie (TWIN) Foundation, Erasmus MC University Medical Centre, Maastricht University Medical Centre and Amsterdam University Medical Centre.

**Competing interests** Amsterdam University Medical Centre received funds from Stryker for consultations by Professor Dr Majoie, Professor Dr Roos and Dr Berkhemer. Maastricht University Medical Centre received funds from Stryker and Codman for consultations by Professor Dr Van Zwam. Dr Nederkoorn: Grants from CVON/Dutch Heart Foundation and Netherlands Organization of Scientific Research. Professor Dr Majoie: Related: Grants TWIN Foundation; Unrelated: Grants from CVON/Dutch Heart Foundation, Stryker, European Commission, TWIN Foundation, Health Evaluation Netherlands (all paid to institution); shareholder of Nico-lab, a company that focuses on the use of artificial intelligence for medical image analysis (modest). Professor Dr Van der Lugt: Grants from CVON/Dutch Heart Foundation, Dutch Brain Foundation, European Commission, Stryker, Medtronic, Penumbra, Cerenovus, Philips, GE Healthcare, Philips Healthcare all paid to institution. The other authors have no conflicts of interest to declare.

**Patient consent for publication** Not applicable.

**Ethics approval** The medical ethics committee of the Erasmus University Medical Centre Rotterdam (the Netherlands) evaluated the study and granted permission to carry out the study as an observational registry (MEC-2014-235). All study protocols and procedures were conducted in accordance with the Declaration of Helsinki and institutional guidelines.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available. Data will not be made available to other researchers as no patient approval has been obtained for sharing data. Syntax files will be made available from the corresponding author on reasonable request.

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## REFERENCES

- 1 Grigoryan M, Haussen DC, Hassan AE, *et al.* Endovascular treatment of acute ischemic stroke due to tandem occlusions: large multicenter series and systematic review. *Cerebrovasc Dis* 2016;41:306–12.
- 2 Jovin TG, Chamorro A, Cobo E, *et al.* Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015;372:2296–306.
- 3 Rubiera M, Ribo M, Delgado-Mederos R, *et al.* Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis. *Stroke* 2006;37:2301–5.
- 4 Jadhav AP, Zaidat OO, Liebeskind DS, *et al.* Emergent management of tandem lesions in acute ischemic stroke. *Stroke* 2019;50:428–33.
- 5 Dufort G, Chen BY, Jacquin G, *et al.* Acute carotid stenting in patients undergoing thrombectomy: a systematic review and meta-analysis. *J Neurointerv Surg* 2021;13:141–5.
- 6 Papanagiotou P, Haussen DC, Turjman F, *et al.* Carotid stenting with antithrombotic agents and intracranial thrombectomy leads to the highest recanalization rate in patients with acute stroke with tandem lesions. *JACC Cardiovasc Interv* 2018;11:1290–9.
- 7 Wilson MP, Murad MH, Krings T, *et al.* Management of tandem occlusions in acute ischemic stroke - intracranial versus extracranial first and extracranial stenting versus angioplasty alone: a systematic review and meta-analysis. *J Neurointerv Surg* 2018;10:721–8.
- 8 Maus V, Borggrefe J, Behme D, *et al.* Order of treatment matters in ischemic stroke: mechanical thrombectomy first, then carotid artery stenting for tandem lesions of the anterior circulation. *Cerebrovasc Dis* 2018;46:59–65.
- 9 Rangel-Castilla L, Rajah GB, Shakir HJ, *et al.* Management of acute ischemic stroke due to tandem occlusion: should endovascular recanalization of the extracranial or intracranial occlusive lesion be done first? *Neurosurg Focus* 2017;42:E16.
- 10 Poppe AY, Jacquin G, Stapf C, *et al.* A randomized pilot study of patients with tandem carotid lesions undergoing thrombectomy. *J Neuroradiol* 2020;47:416–20.
- 11 Kang D-H, Kim Y-W, Hwang Y-H, *et al.* Endovascular recanalization of acute tandem cervical carotid and intracranial occlusions: efficacy of cervical balloon angioplasty alone then intracranial target recanalization strategy. *World Neurosurg* 2019;126:e1268–75.
- 12 Lockau H, Liebig T, Henning T, *et al.* Mechanical thrombectomy in tandem occlusion: procedural considerations and clinical results. *Neuroradiology* 2015;57:589–98.
- 13 AbuRahma AF, Avgerinos ED, Chang RW, *et al.* Society for vascular surgery clinical practice guidelines for management of extracranial cerebrovascular disease. *J Vasc Surg* 2022;75:4S–22.
- 14 Yu S, Liebeskind DS, Dua S, *et al.* Postischemic hyperperfusion on arterial spin labeled perfusion MRI is linked to hemorrhagic transformation in stroke. *J Cereb Blood Flow Metab* 2015;35:630–7.
- 15 Kirchoff-Torres KF, Bakradze E. Cerebral hyperperfusion syndrome after carotid revascularization and acute ischemic stroke. *Curr Pain Headache Rep* 2018;22:24.
- 16 Heck DV, Brown MD. Carotid stenting and intracranial thrombectomy for treatment of acute stroke due to tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage. *J Neurointerv Surg* 2015;7:170–5.
- 17 Zhu F, Labreuche J, Haussen DC, *et al.* Hemorrhagic transformation after thrombectomy for tandem occlusions. *Stroke* 2019;50:516–9.
- 18 Anadani M, Spiotta AM, Alawieh A, *et al.* Emergent carotid stenting plus thrombectomy after thrombolysis in tandem strokes: analysis of the titan registry. *Stroke* 2019;50:2250–2.
- 19 Jansen IGH, Mulder MJHL, Goldhoorn R-JB, *et al.* Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR clean registry). *BMJ* 2018;360:k949.
- 20 Berkhemer OA, Borst J, Kappelhof M, *et al.* Extracranial carotid disease and effect of intra-arterial treatment in patients with proximal anterior circulation stroke in MR clean. *Ann Intern Med* 2017;166:867–75.
- 21 Tan IYL, Demchuk AM, Hopyan J, *et al.* CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. *AJNR Am J Neuroradiol* 2009;30:525–31.
- 22 van Swieten JC, Koudstaal PJ, Visser MC, *et al.* Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604–7.
- 23 Higashida RT, Furlan AJ, Roberts H, *et al.* Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke* 2003;34:e109–37.
- 24 von Kummer R, Broderick JP, Campbell BCV, *et al.* The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke* 2015;46:2981–6.
- 25 VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol* 2019;34:211–9.
- 26 Anadani M, Marnat G, Consoli A, *et al.* Endovascular therapy of anterior circulation tandem occlusions: pooled analysis from the titan and ETIS registries. *Stroke* 2021;52:STROKEAHA120033032..
- 27 Bonati LH, Kakkos S, Berkefeld J, *et al.* European stroke organisation guideline on endarterectomy and stenting for carotid artery stenosis. *Eur Stroke J* 2021;6:1–XLVII.
- 28 Naylor AR, Ricco J-B, de Borst GJ, *et al.* Editor's Choice - 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;55:3–81.