Carotid endarterectomy for symptomatic low-grade carotid stenosis

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Objective: **Although the management of carotid disease is well established for symptomatic lesions ≥70%, the surgical treatment for a symptomatic ≤50% stenosis is not supported by data from randomized trials. Factors other than lumen narrowing, such as plaque instability, seem to be involved in cerebral and retinal ischemic events. This study analyzes the early-term and long-term outcomes of carotid endarterectomy (CEA) performed in patients with low-grade (≤50% on North American Symptomatic Carotid Endarterectomy Trial criteria) symptomatic carotid stenosis.**

Methods: **The study involves 57 consecutive patients undergoing CEA for symptomatic low-grade carotid disease at our institution over 5 years, and 21 (36.8%) had experienced more than one ischemic event. Overall, 48 (84.2%) had a minor stroke, and nine (15.8%) had an episode of retinal ischemia. Diagnosis was made by a vascular neurologist based on an ultrasound examination combined with noninvasive imaging studies, after ruling out other possible causes of embolization. Before CEA, all patients were receiving antiplatelet treatment, and 87% were taking statins. All patients underwent eversion CEA under general deep anesthesia, with selective shunting. All carotid plaques were examined histologically. Long-term follow-up (median, 28 months; mean, 32 ± 5 months; range, 3-56 months) was obtained for 55 patients.**

Results: **No 30-day strokes or deaths occurred, and no patients had recurrent neurologic events related to the revascularized hemisphere during the follow-up. No late carotid occlusions were detected, but one asymptomatic moderate restenosis was documented. There were seven late deaths (12.7%), none of which were stroke-related. Survival rates were 98% at 1 year and 90% at 3 years. All removed carotid plaques showed different features of ulceration or rupture, with underlying hemorrhage associated with a thrombus.**

Conclusions: **This study shows that CEA is a safe, effective, and durable treatment for patients with symptomatic low-grade carotid stenosis associated with unstable plaque. Patients had excellent protection against further ischemic events and survived long enough to justify the initial surgical risk. Plaque instability seems to play a major part in the onset of ischemic events, regardless the entity of lumen narrowing. (J Vasc Surg 2014;59:25-31.)**

Carotid disease accounts for 10% to 20% of all ischemic strokes,[1,2] and generally speaking, the pathogenetic substrate of stroke attributable to carotid pathology is a plaque that causes hemodynamic turbulences ascribable to area reduction and with a complicated structure and surface generating emboli or determining occlusion. Guidelines for the best management of symptomatic internal carotid artery stenosis are based mainly on the conclusions of large randomized clinical trials (RCTs) such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[3] and the European Carotid Surgery Trial (ECST).[4] Pooled data from these RCTs demonstrated that carotid endarterectomy (CEA), compared with best medical management, is highly beneficial for individuals with cerebrovascular symptoms attributable to a carotid luminal narrowing ≥69% on angiography, with a 16% lower 5-year absolute risk of ipsilateral ischemic stroke. For symptomatic patients with moderate (50%-69%) carotid stenosis, the risk reduction is only 4.6%, and the benefit of CEA is minimal for symptomatic patients with mild (30%-49%) carotid stenosis.[5]

There is a consensus that medical therapy is as efficient as surgery for symptomatic patients with ≤50% carotid stenosis, but the presence of a vulnerable plaque, confirmed by well-established ultrasound criteria, might place these patients at a higher risk of cerebral ischemic events recurrence. As determined from results of RCTs, surgery does little to reduce the risk of ipsilateral ischemic stroke for low-grade (≤50%) symptomatic stenosis, not because patients are risk-free but because the surgical risk exceeds the stroke risk with medical management. Stroke risk and the benefits of CEA both increase with higher degrees of stenosis; thus, carotid narrowing is nowadays the most validated stroke risk parameter on which management decisions are based.[6]

The optimal approach for managing lower degrees of carotid disease remains unclear, however.[7] Several studies have shown that severe stenotic lesions might remain asymptomatic for many years on best medical treatment,[8]

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whereas lower degrees of stenosis might progress and lead to a cerebral ischemic event over a short period of time due to plaque complication.[9-11]

In the last few years, progressive improvement has occurred in ultrasound B-mode imaging and in ultrasound contrast agents, and ultrasound B-mode is presently the best method for demonstrating low-grade carotid stenosis.[12] Although velocity measurements rule out a more severe stenosis, B-mode imaging in the longitudinal and cross-sectional planes is more relevant than velocity values in low-grade disease. Furthermore, the measurement of area reduction is more accurate than diameter reduction, especially when confronted with plaques with an irregular surface.[13,14]

In recent years, there has been a growing interest in multiparameter carotid plaque assessment, placing less emphasis on the degree of stenosis and more on its morphology, mobility, and composition. Intraplaque hemorrhage (IPH) and thin, ulcerated, or ruptured fibrous caps seem to be associated with higher stroke risk,[15-20] supporting the hypothesis, as in coronary artery disease, that many cerebral infarctions result from distal embolization,[21-23] not hypoperfusion, as it occurs distally to severe lesions or occlusions.[24,25]

This study was conducted to prospectively analyze the early-term and long-term outcomes of CEA performed outside the current guidelines in symptomatic patients with low-grade carotid lesions, assessing the morphologic and histologic features of the removed carotid plaques.

METHODS

The University of Padua, School of Medicine Ethics Committee approved the study. All patients gave their written informed consent to analyzing their records and publishing the findings.

Patients. A prospectively compiled computerized database was queried concerning all patients undergoing CEA at our tertiary referral center between January 2008 and December 2012 for recently symptomatic (<2 months) carotid plaque causing a ≤50% stenosis according to the NASCET criteria.[3] All patients were already receiving antiplatelet treatment, and most were taking statins before they were enrolled.

After their first ever ipsilateral or recurrent cerebral ischemic event, or plaque progression/instability, they entered the study and underwent CEA. Patients were routinely monitored for the first 3 days of their hospital stay. They underwent transthoracic and transesophageal echocardiography and were finally examined by a consultant cardiologist to rule out any cardiac source of embolization. A vascular neurologist attributed all cerebral or retinal ischemic events to embolization from an ipsilateral carotid stenosis. All patients were diagnosed with symptomatic carotid lesions ≤50% based on velocity criteria (peak systolic velocity <125 cm/s) on preoperative duplex ultrasound performed by two experienced neurosonographers.[26]

Carotid plaque morphology and characteristics were analyzed using contrast-enhanced carotid ultrasonography. Plaque morphology in terms of echogenicity, defined with reference to the sternocleidomastoid muscle, was assessed in a modified version of the classification proposed by Gray-Weale et al[27] and graded from 1 to 4 as echolucent, predominantly echolucent, predominantly echogenic, or echogenic.[19] Unstable plaque was defined on carotid ultrasound as echolucent or heterogeneous plaque, with surface irregularities, ulcer, or rupture. Plaque inflammation, adventitial vasa vasorum, intimal angiogenesis, and plaque neovascularization were identified on contrast-enhanced carotid ultrasonography as potential indicators of atheroma instability.

All patients underwent additional noninvasive imaging,[28] including magnetic resonance imaging (MRI)/angiography, computed tomography angiography, or digital subtraction angiography, to exclude tandem lesions (ie, a second intracranial lesion on the same vessel) and to confirm the decision to perform CEA. Transcranial color-coded Doppler sonography was also performed in all patients to assess vasomotor reactivity and any intracranial atherosclerotic lesions or intracranial compensatory collaterals.

The patients' demographic and clinical data were recorded on a standardized form, including potential atherosclerotic risk factors, several risk-related characteristics, such as cholesterol, high-density lipoprotein cholesterol, triglycerides, or homocysteine, anatomic and clinical variables, preoperative medication, details of surgery, and all perioperative outcomes. The consultant neurologist assessed all patients preoperatively, on waking from the anesthesia, before discharge from the hospital, and during the follow-up. All patients with diabetes or hyperlipidemia, or both, and those with prior ischemic events were receiving statin therapy.

Surgical procedure. All surgical procedures were eversion CEAs performed by the same surgeon, with patients under general anesthesia, and routine intraoperative electroencephalographic monitoring was used for selective intraluminal shunting. The technical details of the surgical procedure have been described elsewhere.[29] Shunting depended exclusively on electroencephalographic changes consistent with cerebral ischemia occurring during carotid cross-clamping and unrelated to any bradycardia or arterial hypotension. Patients were administered intravenous unfractionated heparin (5000 U) before carotid clamping. Heparinization was never reversed with protamine up until December 2009; from January 2010 onward, all patients had partial (half-dose) heparin reversal. No completion angioscopy or imaging studies were performed.

Patients were usually monitored in the recovery room for 2 hours until their blood pressure and neurologic status were judged acceptable and then were transferred to a nursing unit specialized in vascular care for 12 to 24 hours. Patients with severe headache were closely monitored for hyperperfusion syndrome, and hypertension was treated aggressively. Most patients were discharged 48 to 72 hours after CEA.

Histopathologic analysis. All everted plaques were removed en block, with no longitudinal incision (to eliminate the potential for artifact), and immediately fixed in formalin. The plaque was cut transversally to the longitudinal lumen into 5-μm sections for embedding in paraffin. Four adjacent 5- to 10-μm thick sections were taken from each block and stained/immunostained with (1) hematoxylin and eosin, (2) elastin van Gieson to assess the fibroelastic component, (3) CD68 antibody for macrophages, and (4) CD3 antibody for lymphocytes.

Histologic features. For each plaque, the following features were considered:

1. Ulceration of the fibrous cap in a setting of endothelial cells disruption;
2. Plaque rupture in a setting of disruption or complete clear communication between the lipid core and the lumen, usually at a point of fibrous cup thinning or inflammation, or both;
3. Lipid core size, defined as the area of amorphous material containing cholesterol crystals out of the total area of the plaque;
4. Calcification—judged to be in large amounts when nodular deposits were seen (nodular calcification) or in small amounts when there was only stippling—and its location within the plaque;
5. Neovascularization, when small vessels or capillaries were identified mostly within loose extracellular matrix;
6. Type and location of inflammatory cell infiltrate within the plaque;
7. Percentage of fibrous tissue out of the total area of plaque;
8. IPH, including recent or earlier hemorrhage, defined as evidence of erythrocytes or erythrocyte debris in the plaque disrupting its architecture; and
9. Mural or occlusive thrombus, recorded in the setting of nonocclusive or occlusive thrombus in the lumen, characterized by platelets, fibrin strands, and white and red blood cells.

The type of atherosclerotic plaque was recorded according to the American Heart Association/Virmani classification.[30]

Surveillance protocol. After discharge, nurses monitored the patients' vital parameters. The consultant neurologist systematically performed a physical and neurological assessment of all surviving patients. Post-CEA duplex ultrasound scans were performed by two experienced neurosonographers at 1, 6, and 12 months, and then yearly, assessing any carotid restenosis or late occlusions. Neurologic events were always classified by the consultant neurologist as:

- Transient ischemic attacks (TIAs), defined as temporary hemispheric symptoms lasting ≤24 hours, with complete recovery;
- Amaurosis fugax, noted as transient monocular visual loss;
- Minor stroke, a clinical syndrome of rapidly developing signs or symptoms of focal loss of cerebral function of vascular origin lasting >24 hours but not leading to any handicap or significant impairment in activities of daily living, assessed as <3 on the modified Rankin-scale[31]; or
- Major stroke, defined as a focal neurologic deficit lasting >30 days and inducing a change in lifestyle, assessed as 3/5 on the modified Rankin scale.

Brain imaging (computed tomography or MRI) was performed in all patients with new neurologic deficits after CEA. Cardiac complications were classified by the same cardiologist and included (1) myocardial infarction diagnosed from creatinine kinase-MB levels and electrocardiogram findings, (2) pulmonary edema confirmed by chest X ray imaging, (3) documented ventricular fibrillation or primary cardiac arrest, and (4) new congestive heart failure, requiring a pacemaker. A postoperative electrocardiogram was obtained routinely in all patients with a history of coronary artery disease, congestive heart failure, or arrhythmia (rhythm other than sinus), and cardiac isoenzymes were tested in all patients with new findings on the postoperative electrocardiogram. Other complications and events observed during the follow-up were recorded in accordance with the guidelines of the Ad Hoc Committee on Reporting Standards for Cerebrovascular Disease, Society for Vascular Surgery/North American Chapter of the International Society of Cardiovascular Surgery.[32]

End points were perioperative stroke and death, nonrecurrence or relief of hemispheric symptoms, carotid restenoses or late occlusions, and stroke-free survival rates.

Statistical analysis. The statistical analysis was performed with SSPS 12.0.1 software (SPSS Inc, Chicago, Ill). The patients' demographic data are given as medians, means and ranges, and baseline clinical and diagnostic findings as incidence rates. Survival rates were calculated with the Kaplan-Meier method and reported as life-table analyses. Significance was assumed at $P < .05$.

RESULTS

During the study period, 369 CEAs were performed at our institution in 321 patients for symptomatic and asymptomatic carotid lesions based on the NASCET[3] and the Asymptomatic Carotid Atherosclerosis Study (ACAS)[33] recommendations. An additional 57 patients had 57 CEAs for symptomatic ≤50% carotid stenoses and formed our study population. None of the CEA procedures considered here were aborted or incomplete, and none of the patients were refused CEA for technical reasons emerging during the surgery. The preoperative characteristics of the patients are summarized in Table I.

Before CEA, 3 patients had experienced 4 ischemic events, 7 patients 3 events, 11 patients 2 events, and the other 36 patients only 1 event. The event prompting CEA or, for patients with multiple events their last ischemic event was a minor ischemic stroke in 48 patients and a retinal ischemia in nine. At the time of their ischemic

Table I. Patient demographics, risk factors, clinical presentation, time of surgery from the last ischemic event, and preoperative medical treatment

Variables	*No. (%) or mean ± SD*
Preoperative characteristics	
Patients/surgical procedures	57 (100)
Male gender	38 (66.7)
Age, years	74.6 ± 2.8
<70	10 (17.5)
70-80	41 (71.9)
>80	6 (10.5)
Risk factors	
Hypertension	38 (66.7)
Smoking	42 (73.6)
Diabetes	19 (33.3)
Hyperlipidemia	30 (52.6)
Cardiac disease	20 (36.8)
Chronic kidney disease	3 (5.2)
Pulmonary disease	7 (12.3)
Peripheral atherosclerotic disease	32 (56.1)
Symptoms	
Stroke	48 (84.2)
Retinal ischemia	9 (15.8)
Time of CEA from the last ischemic event, weeks	
2	42 (3.7)
3	8 (14.0)
4	3 (5.3)
8	4 (7.0)
Preoperative medications	
Antithrombotic therapy	57 (100)
Aspirin	20 (36.8)
Ticlopidine	9 (15.8)
Aspirin and clopidogrel	17 (29.8)
Clopidogrel	8 (14.0)
Warfarin	3 (5.3)
Statin therapy	49 (86.0)

CEA, Carotid endarterectomy; *SD,* standard deviation.

Table II. Selected risk-related variables stratified by plaque echogenicity

Variable[a]	*Echolucent (n = 16)*	*Predominantly echolucent (n = 41)*
Cholesterol, mmol/L	7.45 ± 1.23	7.34 ± 1.32
HDL cholesterol, mmol/L	1.37 ± 0.35	1.38 ± 0.40
Triglycerides, mmol/L	2.06 ± 1.12	2.09 ± 1.09
Homocysteine, μmol/L	11.5 (7.8-40.7)	11.6 (8.3-41.8)

HDL, High-density lipoprotein.
[a]Values are presented as unadjusted means ± standard deviation or median (range).

Table III. Plaque features stratified by clinical presentation

Variable	*Stroke (n = 48), No. (%)*	*Retinal ischemia (n = 9), No. (%)*	*Total (N = 57), No. (%)*
Type of plaque			
Fibrous	15 (31.2)	2 (22.2)	17 (29.8)
Atheromatous	33 (68.8)	7 (77.8)	40 (70.2)
Thrombotic active plaque	48 (100)	9 (100)	57 (100)
Fibrous cap			
Rupture	33 (68.8)	7 (77.8)	40 (70.2)
Ulceration	15 (31.2)	2 (22.2)	17 (29.8)
IPH	41 (85.4)	8 (88.9)	49 (86)
Thrombus			
Mural	27 (56.2)	3 (33.3)	30 (52.6)
Occlusive	20 (41.7)	5 (55.6)	25 (43.8)
Calcification			
Nodular	32 (66.7)	6 (66.6)	38 (66.7)
Mild	12 (25)	2 (22.2)	14 (24.6)
Neovascularization	21 (43.7)	5 (55.6)	26 (45.6)

IPH, Intraplaque hemorrhage.

event (or their last event in patients with multiple ischemic events), all patients were taking antiplatelet drugs or antithrombotic therapy (20 aspirin, 9 ticlopidine, 17 aspirin and clopidogrel, 8 clopidogrel only, and 3 warfarin due to prior atrial fibrillation) and 49 (86%; all patients who had 1 ischemic event, 6 who had 3 events, 6 who had 2 events, and 1 who had 4 events) were also taking statins. CEA was performed in 42 patients within 2 weeks of their (last) ischemic event, in 8 within 3 weeks, in 3 within 1 month, and in the remaining 4 within 2 months (Table I). Some risk-related characteristics stratified by plaque echogenicity are reported in Table II.

Perioperative (30-day) results. No perioperative strokes, deaths, or cerebral hemorrhages occurred in this series. One transient neurologic deficit (1.7%) ipsilateral to the revascularized hemisphere resolved ≤24 hours postoperatively in a patient with a contralateral carotid occlusion. Two minor complications (3.5%) occurred: one patient had neck bleeding not requiring surgical evacuation, and one had a temporary hypoglossal nerve injury that completely recovered spontaneously ≤30 days.

Histologic analysis revealed various features of ulceration or rupture of the atherosclerotic plaques with underlying IPH associated with a fresh thrombus, confirming preoperative ultrasound findings and MRI images evocative of unstable plaque (Table III).[7]

Long-term outcomes. Long-term follow-up was obtained in all but two patients (median, 28 months; mean, 32 ± 5 months; range, 3-56 months). No patients had any recurrent neurologic event relating to the revascularized hemisphere.

No late carotid occlusions were detected in this series. One moderate restenosis (between 50% and 70%) without symptoms was identified ≤24 months after CEA, which remained stable at subsequent duplex ultrasound scans and was treated conservatively.

Seven late deaths (12.7%) occurred, none of them stroke-related, at a mean of 30 months after CEA: four patients died of myocardial infarction (none had coronary artery disease at the time of CEA or perioperative cardiac events), two of malignancy, and one after a car accident. Kaplan-Maier life-table analysis showed that the survival

rates were 98.2% ± 1.7% (95% confidence interval, 1.491-1.978) at 1 year, with 45 patients at risk, and 90.2% ± 4.4% (95% confidence interval, 3.838-5.157) at 3 years, with 22 patients at risk.

DISCUSSION

The present study shows that patients with low-grade carotid stenosis may develop medically refractory ischemic events in the presence of unstable plaque, identifiable using noninvasive diagnostic tools, and that CEA is a safe, effective, and durable procedure in such cases. No major ischemic events or deaths occurred perioperatively, and no patients had recurrent cerebrovascular events related to the revascularized hemisphere or died of stroke during the follow-up. No late carotid occlusions were detected, and a moderate restenosis was only identified in 1.8% of the endarterectomized vessels. On the basis of current guidelines, which focus mainly on the severity of carotid lumen narrowing, surgical management would not be recommended in such symptomatic patients due to the minimal balance between benefits and risks of CEA.[3-5]

Low-grade carotid lesions are often disregarded as potential causes of cerebral embolization because of presumed coexisting diseases (eg, atrial fibrillation) and because the size of the plaque may be underestimated as a consequence of vascular remodelling.[7] Evaluating the stroke risk by the degree of stenosis alone may not suffice; additional parameters are needed to better identify subgroups of high-risk patients who would benefit more from surgery.[7,28,34] Plaque morphology, regardless of lumen narrowing, seems to influence the likelihood of adverse ischemic events as well as being a valid predictor of ipsilateral stroke, the unstable plaque being an intriguing entity that has been inconclusively studied with contradictory results.[15-20]

Ultrasound evaluation combined with noninvasive cerebral imaging studies has proved valuable for characterizing plaque and assessing stroke risk.[19,35-37] All of our patients' low-grade carotid plaques showed signs of instability: histology revealed a ruptured or ulcerated fibrous cap with underlying IPH, associated with a fresh thrombus within the lumen. Similar findings were recently reported in 127 patients with unstable plaque who underwent CEA[38]: acute thrombotic plaques were significantly more associated with stroke than with TIA or asymptomatic individuals and involved more ulcerated (73%) than ruptured plaques (27%).[39] These lesions occurred mainly in carotid segments with nonsignificant stenosis (≤50%), whereas healed lesions prevailed in segments with >70% luminal narrowing.[38]

The finding that rupture occurs more frequently in lower grades of stenosis is not new[7,39] and is consistent with Laplace's law, which states that more pressure is exerted on the fibrous cap of a nonsignificant lesion than on severe stenotic plaques.[23] In a landmark article on the role of carotid plaque rupture and thrombosis in the pathogenesis of ischemic stroke in patients who underwent CEA for symptomatic and asymptomatic severe carotid lesion, Spagnoli et al[20] found a fresh thrombus at the site of the ruptured cap in all plaques removed ≤2 months of symptoms onset, whereas different stages of organized thrombosis were seen in plaques removed 3 to 22 months after the event, suggesting that thrombosis of the ruptured plaque plays a fundamental part in the pathogenesis of cerebral symptoms, probably due to artery-to-artery microembolism arising from the thrombotic lesion.

About one-third of our patients had more than one ischemic event before CEA. This correlates well with the demonstration that the initiating ischemic event involves rupture of the plaque, which then remains unstable for up to 2 years[20] and susceptible to further superficial cap erosion or rupture and thrombosis, predisposing patients to a continuous release of emboli in the distal cerebral territory.[20] Salem et al[40] confirmed as much by showing that plaques excised from patients within 1 to 2 weeks of their last clinical event had more unstable features, which diminished with time (over 3 weeks), then increased again. None of our patients had ischemic events during their follow-up, which underscores the significant role of unstable plaque, whatever its extent, in the pathogenesis of ischemic cerebral events. Our findings coincide with those of a retrospective study of 31 patients with symptomatic ≤70% carotid stenosis on noninvasive imaging but who nonetheless underwent CEA: macroscopically, all removed plaques revealed plaque rupture with IPH, and none of the patients had further ischemic events after CEA.[28]

As in other studies,[40] we offered CEA to patients refractory to multidisciplinary medical treatment, including patients with cerebral/retinal ischemia or carotid plaque progression, regardless of aggressive risk-factor control plus full antithrombotic treatment, plus high-dose statin therapy. All patients received antiplatelet or anticoagulant treatment before surgery and had IPH underlying discontinuous or ruptured fibrous cap. It is not clear whether antithrombotics might have exacerbated bleeding into the plaque, thereby hastening cap erosion or rupture and acute thrombus formation, and this matter would warrant further investigation.

Our findings should be interpreted bearing the study's limitations in mind. First, although the analysis was prospective, the sample was relatively small and concerned a single institution and the same surgeon.

Second, the similar features seen in the carotid plaques may stem from the fact that all patients underwent surgery relatively soon after their ischemic event as a result of efforts to expedite CEA for symptomatic patients whenever possible.

Third, we agree that microembolic signal detection by transcranial Doppler is a surrogate marker of carotid plaque activity and progression of the lesion and is positively associated with a greater embolic potential of the plaque and a higher stroke recurrence rate. It is a very long procedure, however, needing multiprobe monitoring. The most accurate technique requires an experimental carotid microembolic signal detector, which we do not have.

Fourth, this study would have benefited from a comparison with outcomes in patients with symptomatic low-grade stenosis followed up with the best medical treatment instead of CEA, but it seemed unethical to keep patients on medication if CEA was indicated.

Finally, we are aware that the absence of perioperative and late major or minor neurologic complications or stroke-related deaths among our patients might denote relative lack of power, limiting the reliability of the results.

CONCLUSIONS

This prospective study showed that CEA is a safe, effective, and durable option for treatment of patients with symptomatic carotid low-grade stenosis associated with unstable plaque. Patients had excellent protection against further ischemic events and survived long enough to justify the initial surgical risk. Plaque instability seems to play a major part in the occurrence of ischemic events, irrespective of lumen narrowing.

AUTHOR CONTRIBUTIONS

Conception and design: EB, AA, CB
Analysis and interpretation: EB, AA, CB
Data collection: GP
Writing the article: EB, CB
Critical revision of the article: EB, AA, AT, CB
Final approval of the article: EB, AA, FM, GP, AT, CB
Statistical analysis: FM
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