A 16-year experience of carotid artery stenting for carotid artery stenosis

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AIM: *We report our experience of carotid artery stenting (CAS) for the endovascular treatment of significant carotid stenosis over 16 years.*
MATERIALS AND METHODS: *Data of all consecutive patients who came for a significant carotid artery stenosis from January 1st 1999 to August 31st 2015 were retrospectively collected and analyzed. Primary outcomes were the occurrence of death and major cerebrovascular events (MCE) both at 30-day and at long-term.*
RESULTS: *In our experience CAS was a safe and effective technique, with acceptable mortality and neurological complication rates, both at 30 days and in the long term.*

KEY WORDS: Carotid stenting, Carotid stenosis, Long-term follow-up

Introduction

Carotid endarterectomy (CEA) has been considered worldwide the standard treatment for severe asymptomatic and symptomatic carotid stenosis for more than 50 years. Carotid artery stenting (CAS) has emerged in the last 15 years as an alternative to surgery, especially in high-risk patients [1]. CAS has been slowly gained widespread approval and many randomized trials have been published to assess the superiority of one method over the other [2]. However trial findings have generated more heat than light, as controversy and bias have connected to the interpretation of their results.

These randomized studies in fact were burdened by several limitations, the most important being the limited endovascular expertise requirements for operators performing CAS [3] and the second being the fact that they were performed about 10 years ago.
In this sense, large scale registries and case series with long-term outcomes are more representative of a real world experience, reflecting what routinely happens in the clinical practice.
In our Operative Unit of Vascular Surgery, CAS has been offered since 1999 as an alternative to CEA for the treatment of both symptomatic and asymptomatic carotid artery stenosis in moderate-to-high risk patients. We report our retrospective experience, with some tips and tricks learned over 16 years.

Materials and Methods

The study was approved by the Institutional Review Board.
Data of all consecutive patients who came to our Division for a severe carotid artery stenosis from January 1st 1999 to August 31st 2015 were retrospectively collected from medical records and patients' imaging.

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Patients' records were reviewed for personal data (age, sex), presence of cardiovascular risk factors (diabetes mellitus, hypertension, dyslipidemia, chronic renal failure, ischemic heart disease, smoking, familiar history of cardiovascular disease, obesity, any previous stroke), preoperative neurologic symptoms within the previous six months, side of the lesion, etiology of the lesion (primary stenosis/post-surgical restenosis/in-stent restenosis), features of the plaque and any contralateral carotid occlusion. Intraoperative data included the use of any cerebral protection device, pre- and post-dilatation, operation time, the amount of contrast used, procedural success (defined as the completion of the procedure with a residual stenosis <30% [4]), the occurrence of cerebral ischemic events and intraoperative complications. Follow-up data were obtained from reports of outpatient visits and through telephonic interview (occurrence of cerebrovascular events and death). Imaging was performed every 3 months during the first year after the operation and annually thereafter using duplex scans to record the occurrence of either restenosis or stent occlusion. The occurrence of death, and major cerebrovascular events (MCE) were recorded, both at 30-day and at long-term, as primary outcomes. Secondary outcomes were the occurrence of restenosis and the analysis of factors associated to the occurrence of perioperative and long-term complications.

All collected data were inserted in a database and analyzed as appropriate, using the software JMP 5.1.2 (SAS Institute). Continuous variables are reported as median and interquartile range (IQR); categorical variables are presented as n (%). Logistic regression was performed to identify predictors of perioperative and long-term complications, reporting Hazard Ratios (HR) with 95% Confidence Intervals (CI). P values <0.05 were considered statistically significant.

Patients' Selection

In our Operative Unit CEA is the gold standard treatment for significant carotid artery stenosis in low surgical risk patients. CAS is usually offered as an alternative to CEA in both symptomatic and asymptomatic patients who have a moderate-to-high surgical risk but a life expectancy longer than 3 years and having a suitable anatomy for CAS (i.e. absence of severe tortuosity or calcification of the aortic arch or the supra-aortic vessels, soft or hemorrhagic carotid plaques), as reported in Fig. 1.

Since a couple of years, asymptomatic patients who are suitable for both CEA and CAS are randomized to the ACST-2 trials [5].

The anatomical eligibility for CAS is usually established on the basis of a careful preoperative study of the aortic

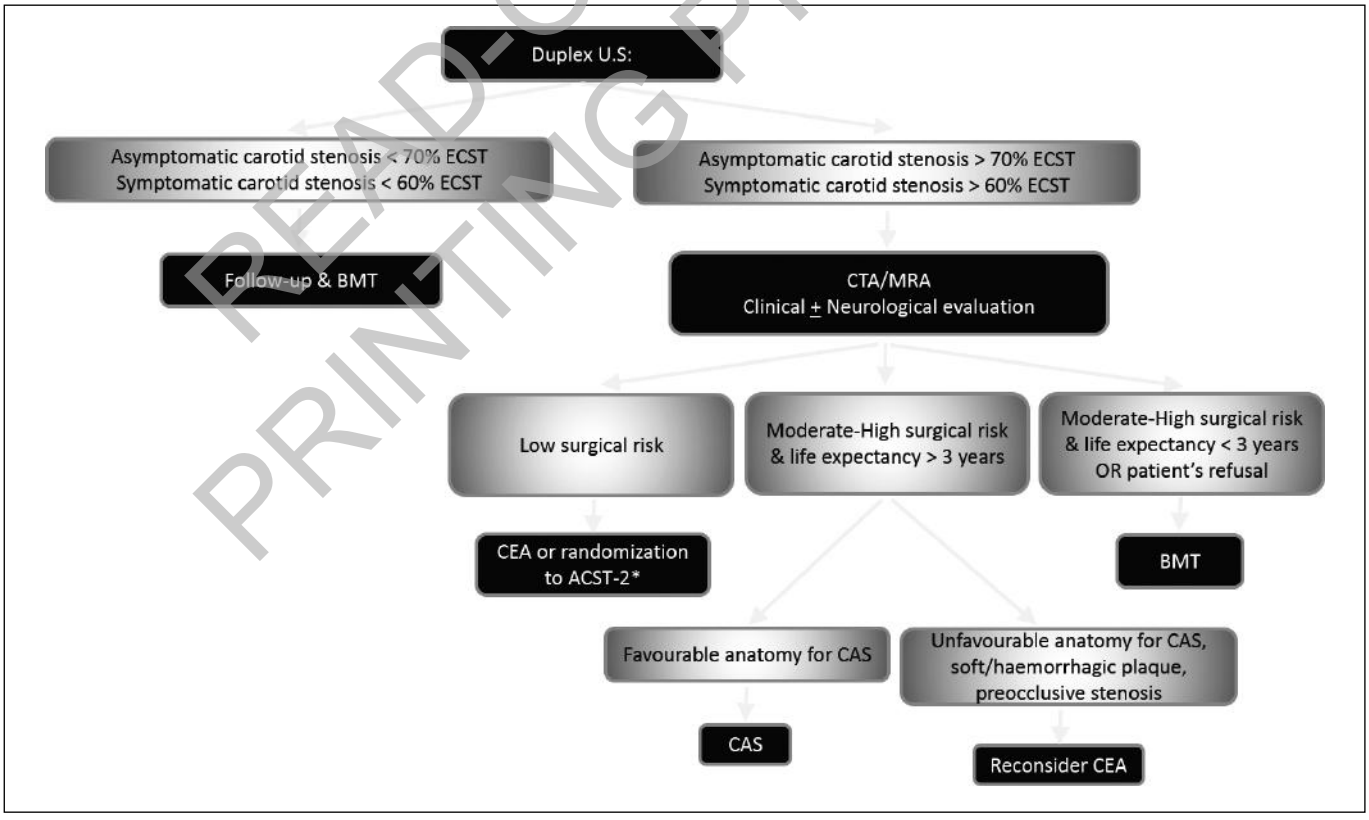


Fig. 1. Flow-chart of the management of significant carotid stenosis in our Operative Unit.

arch and carotid vessels on both duplex scan of the carotid stenosis and a Magnetic Resonance Angiography (MRA) or a Computed Tomographic Angiography (CTA) of the supra-aortic trunks and the intracranial vessels. Femoral arteries are evaluated as well using duplex scan, to assess the presence of any iliac-femoral stenosis or plaque in order to choose the best access for the arterial puncture.
All symptomatic patients usually undergo a preoperative evaluation by expert neurologists.
All procedures are performed in the operating suite by a vascular surgeon, with anesthesiological assistance nevertheless CAS is performed using local anesthesia on the vascular access [6].
A dual oral antiplatelet therapy (usually Aspirin 100 mg daily and Clopidogrel 75 mg daily) is usually started at least 5 days before the endovascular procedure, and continued for one month after revascularization, then aspirin alone (100 mg daily) is continued indefinitely.
Primary stenting is performed whenever possible, using embolic protection devices (EPDs).

Results

A total of 1017 patients (677 males, 66.6%) were treated for either a symptomatic (n=392, 38.5%) or asymptomatic significant carotid stenosis. Their median age was 74 years (IQR 69-79 years).
Patients were mainly affected by hypertension (70.3%), or they had a history of current or previous smoking (61.3%) (Table I).
Most patients were treated for a primitive carotid artery stenosis. In 6 patients, the CAS was a rescue procedure after CEA, either after a failed attempt with an important neurological suffering during the carotid clamping (2 cases) or for a residual distal dissection causing neurological impairment (4 cases).
Technical success was achieved in 99% of the procedures, as four patients required an immediate surgical carotid exploration for an acute stent thrombosis, which was resolved by stent explantation, carotid endarterectomy and carotid patch angioplasty. In the remaining six cases, selective catheterization of the common carotid artery (CCA) was not possible for extreme vessel tortuosity in a bovine type III aortic arch and all patients eventually refused any treatment.
Embolic protection devices (EPDs) were used whenever possible (83.7%), being distal filter in most cases (82.9%), Table II. However in the first period of our experience they weren't routinely used. Primary stenting was performed whenever possible (94.8%).
At 30 days we observed 3 deaths (0.3%) due to a car accident (the patient had a pedestrian collision), cardiac arrhythmia and pulmonary embolism respectively.
Twelve cases of major cerebrovascular events (MCE) occurred within 30 days (1.2%), being 7 cases of ipsilateral minor stroke in symptomatic patients and 5 cases of major stroke. Two of these latter events occurred in patients who were neurologically asymptomatic before the procedure.
At long-term, follow-up was available for 946 patients (93%). The median follow-up period was 81.4 months (range 1 – 200.1 months).
At 5 and 10 years, survival was respectively 86.3%±1.5% and 73.5%±2.3% (Fig. 2), which was significantly affected by history of preoperative neurological symptoms (HR 3.15, 95% CI 2.18-5.49, P=.04) and a duration of the procedure of more than 60 minutes (P=.0017, R2=0.01; Area Under Curve=0.61 at Receiver Operating Characteristic analysis), Table III. Age also was a significant factor affecting long-term survival (P=.04), in particular for patients aged 71 and more at the time of the procedure (AUC 0.54, R^2=0.0065).
Neoplasm was the main cause of death, followed by cardiologic and neurodegenerative diseases. Freedom from stroke (Fig. 3) was 97.1%±0.8% at 5 years (624 at risk)

TABLE I - *Patients' characteristics and anatomical data*

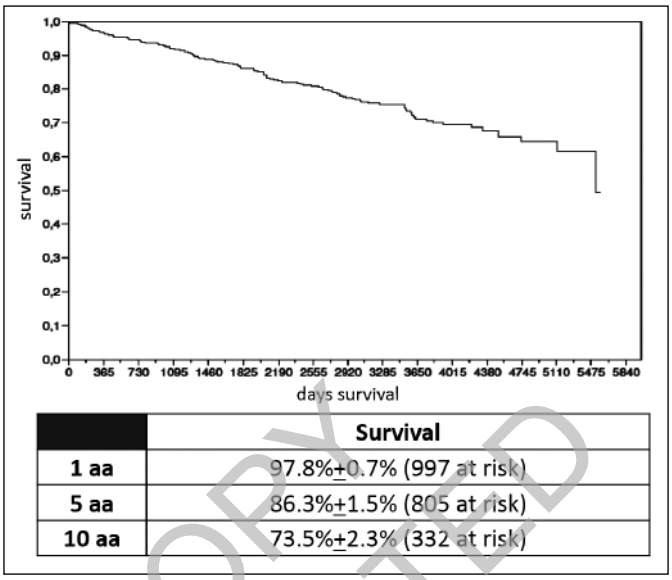
	n = 1017
Male Sex	677 (66.6%)
Median Age, years (IQR)	74 (69 – 79)
Comorbidities	
Current or previous smoke	624 (61.3%)
Coronary artery disease	391 (38.4%)
Hypertension	715 (70.3%)
Dyslipidemia	416 (40.9%)
Diabetes	315 (30.9%)
Obesity	115 (11.3%)
Chronic Renal Failure	92 (9%)
Familiar history of cardiovascular disease	247 (24.3%)
Preoperative symptoms	392 (38.5%)
Any previous stroke (before 6 months)	41 (4%)
Anatomical data (median, IQR)	
Side of the lesion	
Left	548 (53.9%)
Right	469 (46.1%)
Etiology of the stenosis	
Primitive	824 (81%)
In-stent restenosis	7 (0.7%)
Post-CEA restenosis	74 (7.3%)
Rescue of CEA procedures	6 (0.6%)
Contralateral carotid artery	
Mild stenosis	82 (8.1%)
Severe stenosis	71 (7%)
Occluded	152 (14.9%)
Previous CEA/CAS	171 (16.8%)
Features of the carotid plaque	
Ulcerated	89 (8.7%)
Calcified	928 (91.3%)

CCA = Common Carotid Artery
CEA = Carotid Endarterectomy
CAS = Carotid Artery Stenting

TABLE II - *Intraprocedural and in-hospital data (Median, IQR)*

	n = 1017
Procedural success*	1007 (99%)
Embolic Protection Device	
FilterWire EZ	793 (77.9%)
Emboshield/Neuroshield	45 (4.4%)
PAEC	6 (0.6%)
MoMa	2 (0.2%)
Angioguard	5 (0.5%)
Vascular Access Closure	
Manual compression	712 (70%)
Endovascular closure device	305 (30%)
Time of operation (min)	42 (28 – 57)
Amount of contrast (cc)	73 (68 – 83)
Fluoroscopy time (min)	13 (9 – 19)
Length of stay (days)	2 (2 - 3)

*Four acute stent thrombosis which required immediate surgical exploration and 6 failed attempt of selective catheterization of the CCA.



	Survival
1 aa	97.8%±0.7% (997 at risk)
5 aa	86.3%±1.5% (805 at risk)
10 aa	73.5%±2.3% (332 at risk)

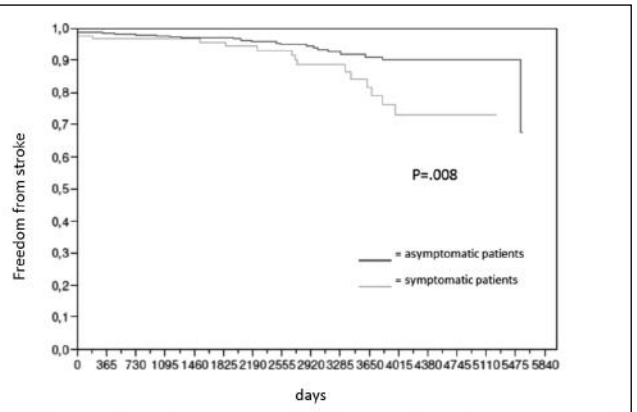
Fig. 2. Overall long-term survival.

TABLE III - *Pearson's correlation for factors significantly associated with the occurrence of death and stroke in the long-term (Hazard Ratios with 95% Confidence Interval; significant P values in bold).*

	Death		Stroke	
	HR (95% CI)	P value	HR (95% CI)	P value
Male sex	1.03 (0.92–2.45)	.06	1.06 (0.84-2.31)	.83
Age	–	**.04**	–	.55
Preoperative symptoms	**3.15 (2.18-5.49)**	**.04**	**2.18 (1.15-4.39)**	**.01**
CAD	2.45 (0.39-4.08)	.23	0.65 (0.23-1.09)	.62
DM	2.18 (0.84-6.25)	.09	1.15 (0.56-2.45)	.4
Hypertension	1.12 (0.98-2.25)	.17	0.72 (0.15-2.27)	.89
Dyslipidemia	0.59 (0.12-3.45)	.36	0.45 (0.09-4.15)	1
CRF	1.03 (0.74-2.26)	.09	1.09 (0.23-3.65)	.86
Stroke >6 months before	1.05 (0.85-1.95)	.77	1.07 (0.21-2.15)	.15
Duration of procedure	–	**.0017**	–	**<.001**
Contralateral carotid occlusion	1.26 (0.11-3.65)	.3	1.82 (0.85-2.27)	.2
EPD	2.11 (0.12-4.38)	.13	3.11 (0.15-5.91)	.09
Ulcerated plaque	1.15 (0.46-3.11)	.09	0.98 (0.21-2.12)	.2
Predilation	0.78 (0.16-3.11)	.4	0.92 (0.11-2.4)	.91
Postoperative stroke within 30 days	1.26 (0.99-2.15)	.06	1.11 (0.65-2.41)	.94
Immediate stent thrombosis	1.07 (0.15-2.24)	.17	1.36 (0.66-2.74)	.44

Legend
HR = Hazard RatioCI = Confidence Interval; CAD = Coronary Artery Disease; DM = Diabetes Mellitus; CRF = Chronic Renal Failure; EPD = Embolic Protection Device

and 91.2%±1.9% at 10 years (240 at risk) respectively for asymptomatic patients, and 95.7%±1.9% at 5 years (180 at risk) and 81.7%±5% at 10 years (90 at risk) respectively at 1 and 5 years for symptomatic patients (P=.008).
The occurrence of MCE was significantly affected by preoperative neurological symptoms (P=.01) and a duration of the procedure which lasted more than 60 minutes (P<.001).
A significant in-stent restenosis > 80% occurred at long-term in 3.8% of patients, one of whom had experienced the occurrence of a TIA. In half of cases, the correction of the restenosis was performed with a redo carotid stenting.



	Asymptomatic	Symptomatic
1 aa	99.1%±0.5% (625 at risk)	97.5%±0.6% (372 at risk)
5 aa	97.1%±0.8% (624 at risk)	95.7%±1.9% (180 at risk)
10 aa	91.2%±1.9% (240 at risk)	81.7%±5% (90 at risk)

Fig. 3. Long-term freedom from stroke in both symptomatic and asymptomatic patients.

Discussion

The treatment of significant carotid artery stenosis has been one of the most discussed topic in the literature so far [2]. Since 1950, carotid endarterectomy (CEA) has been considered the gold standard for the treatment of both symptomatic and asymptomatic carotid stenosis [7]. However the introduction of carotid artery stenting (CAS) as a less invasive alternative in patients deemed to be at high risk for surgery has appealed both physicians and industries to promote and take part into randomized controlled trials which could prove the superiority of one method over the other.

A total of six major trials have randomized 6780 patients to CAS vs. CEA so far [3,8,9,10,11,12]. Data emerging from those trials favored CEA against CAS in terms of perioperative death and stroke rates, however looking for long-term results, no significant differences were found.

Nevertheless trial findings have generated more heat than light, as controversy and bias have been connected to the interpretation of their results. These randomized studies in fact were burdened by several limitations which somehow created lot of concerns.

First, some of these trials had to be stopped before they could reach the target recruiting number, because of high 30-day stroke rates in the CAS arm [10] or because of slow enrolment and lack of funding [9].

Second, most of these trials were performed about 10 years ago, when embolic protection devices (EPDs) were not available or were rarely used and even stents were not used. This was the case of the CAVATAS trials [8].

Third, there was a huge variability among enrolled patients which could create bias and misinterpretation [13].

Last, but not least, physicians could participate to these trial on the basis of limited expertise requirements for operator performing CAS [3].

According to the published guidelines [14], CAS should be performed in centers where the overall stroke and death rates do not exceed 3% for asymptomatic and 6% for symptomatic patients. In the light of this assumption, perioperative death and stroke rates of both CAS and CEA which were reported in the randomized trials seems to be nowadays unacceptable high.

Beyond the results reported in those trials, many experiences of CAS have been reported, sometimes with results similar to those of the RCTs [15]. The main limitation of the registries is that the proportion of symptomatic patients was modest. Overall, the outcomes were favorable, especially if considered that the event rates have decreased over the years parallel to the advancements of technology.

From our experience we have learned that the most important issue to minimize the perioperative event rates after CAS was the appropriate patient's selection on the basis of an accurate preoperative study of the anatomical features of the carotid plaque, the aortic arch and the supra-aortic vessels. Tortuosity of aortic arch and supra-aortic vessels in fact [16], as well as either a soft carotid plaque or a high atherosclerotic burden in the aortic arch itself, would lead to a greater manipulation of catheters and guidewires, with a consequent higher risk of distal embolism in a phase of the procedure when an adequate embolic protection system has not yet been placed. Then, EPDs should be used whenever possible.

Further improvements in CAS technology now on the horizon will likely decrease its periprocedural stroke rates, and that's the main reason why maybe CAS will have a future brighter than that reported up to now.

Conclusions

In our experience, the endovascular treatment of significant carotid artery stenosis by using carotid stenting was a safe and effective technique, with acceptable mortality and neurological complication rates, both at 30 days and in the long term. Preoperative neurological symptoms and a procedure which lasted for more than 60 minutes significantly affected long-term survival and the occurrence of stroke. Mortality was also affected by age. MCE were more likely to occur in patients in whom intraoperative EPDs have not been used.

Riassunto

Da più di 50 anni l'endoarteriectomia carotidea (CEA) è stata considerata il trattamento standard per le stenosi carotidee gravi asintomatiche e sintomatiche. Lo stenting carotideo (CAS) è progressivamente emerso negli

ultimi 15 anni come alternativa alla chirurgia, specialmente nei pazienti ad alto rischio. Da allora, molti studi clinici randomizzati sono stati pubblicati per valutare la superiorità di un metodo rispetto all'altro, tuttavia i risultati dei trials hanno generato più dubbi che certezze nell'interpretazione dei loro risultati, gravati come sono da diverse limitazioni: la principale riguarda la ridotta competenza endovascolare richiesta per gli operatori che hanno eseguito lo stenting carotideo e partecipato ai trials. Inoltre questi trials sono stati eseguiti circa 10 anni fa, con materiali e farmaci differenti rispetto a quelli usati attualmente.

Attualmente i registri su larga scala e le casistiche che riportano risultati a lungo termine sono maggiormente rappresentativi di una esperienza reale, che riflette ciò che accade di routine nella pratica clinica.

Nella nostra Unità Operativa di Chirurgia Vascolare, il CAS è stato offerto dal 1999 come alternativa alla CEA per il trattamento delle stenosi carotidee sintomatiche e asintomatiche nei pazienti a rischio moderato-alto. Scopo del nostro lavoro è di riportare la nostra esperienza retrospettiva, con alcuni consigli e suggerimenti che derivano da ciò che abbiamo imparato in più di 16 anni.

Abbiamo pertanto raccolto e analizzato retrospettivamente i dati di tutti i pazienti consecutivi che sono venuti per una stenosi carotidea significativa dal 1 ° gennaio 1999 al 31 agosto 2015.

I risultati basilari sono stati la mortalità e la morbilità cerebrovascolare maggiore (MCE) sia a 30 giorni che a lungo termine.

Lo studio è stato condotto su 1017 pazienti (677 maschi, 66.6%, età media 74 anni, IQR 69-79 anni) trattati sia per stenosi carotidea sintomatica (n=392, 38.5%) che asintomatica. Il successo tecnico è stato raggiunto nel 99% delle procedure. A 30 giorni abbiamo osservato 3 decessi (0.3%) e 12 MCE (1.2%, 7 dei quali minor stroke e 5 stroke maggiori). A 5 e 10 anni, la sopravvivenza è stata rispettivamente dell'86.3%±1.5% e del 73.5%±2.3%, significativamente influenzata dall'età (P=.04), dalla sintomatologia neurologica preoperatoria (P=.04) e da una durata della procedura maggiore di 60 minuti (P=.0017). La libertà da ictus è stata del 97.1%±0.8% a 5 anni e del 91.2%±1.9% a 10 anni rispettivamente per i pazienti asintomatici, e del 95.7%±1.9% a 5 anni e dell'81.7%±5% a 10 anni rispettivamente per i pazienti sintomatici (P=.008). Il verificarsi di MCE è stato significativamente influenzato dalla sintomatologia neurologica preoperatoria (P=.01) e da una durata della procedura maggiore di 60 minuti (P<.001).

Nella nostra esperienza il CAS è risultato sicuro ed efficace, con tassi di mortalità e di complicanze neurologiche accettabili, sia a 30 giorni che a lungo termine.

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