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CICLO XXXVIII

***THE ROLE OF GENDER, INNOVATIVE TECHNOLOGY AND OF A NOVEL
RISK INDEX IN CAROTID ARTERY STENTING: RESULTS FROM A MULTI-
CENTER STUDY.***

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Dottorando
Dott. Giovanni Mastrangelo

Coordinatore
Prof. Sergio Caputi

Tutor
Prof. Pierluigi Di Sebastiano
Dott. Vincenzo Palazzo

*“Ita fac, mi Lucili: vindica te tibi, et tempus quod adhuc aut auferebatur aut
subripiiebatur aut excidebat collige et serva.”*

*(Fa' così, mio Lucilio: rivendica te stesso a te stesso, e il tempo che finora ti veniva portato via, o ti veniva sottratto, o ti
sfuggiva, raccoglilo e fanne tesoro.)*

Seneca, Epistulae morales ad Lucilium, I, 1

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CHAPTER 1: CAROTID ARTERY STENTING

1.1 INTRODUCTION

Large randomized clinical trials were not designed to analyze and distribute events by gender. Most of the information regarding women was derived from either post hoc analyses or studies, which underrepresented women. Regarding carotid stenting intervention, the impact of gender on procedural outcomes has not yet been well defined. The existing literature has suggested several risk factors, such as vessel diameter, plaque composition, sensitivity to antiplatelet therapy, hormones, as potential mechanisms for gender differences in outcomes after carotid endarterectomy. It has also been shown that atherosclerotic plaque is relatively stable in women, female carotid arteries are high-velocity vessels with an increased inflow/outflow ratio, and they tend to have relatively localized lesions compared to men. These factors are generally associated with favorable short-term and long-term outcomes after carotid endovascular treatment. On the other hand, women tend to have atherosclerotic plaque distributed primarily in the common carotid artery compared to the proximal internal carotid artery, which is usually seen in men. The discrepancy in results between different studies continues to fuel the debate about the possible influence of gender on peri- and post-operative outcomes in CAS. Individualized decision-making based on age, gender, neck anatomy and potential contraindications to CEA or CAS should be taken in high consideration for the optimal selection of carotid revascularization procedures in patients with carotid stenosis. In the last decade, the debate about endovascular solution for carotid artery stenoses was enriched by introduction in market of a new technology for carotid stents, represented by dual-layer micromesh devices, with promising results. This new enthusiasm in carotid artery stenting convinced some authors to openly write about a new, possible, “renaissance”[1] for this technique. Moreover, recent results from a larger international multicentric study [2] had a deflagrating effect on the vascular surgery community about its results. In a sometimes chaotic scientific debate, the search for a personalized medicine interested also carotid artery stenting, in particular for the search for an easy and practical biomarker that can help identify patients. Aim of this doctoral thesis is investigate contemporary Literature about aforementioned themes and discuss clinical results from real-world clinical practice in three tertiary centers for vascular surgery.

1.2 CAROTID ARTERY STENOSIS

Carotid stenosis is a condition characterized by progressive narrowing of the carotid vessel lumen due to atherosclerotic disease or other conditions such as fibromuscular dysplasia, dissection, arteritis, and trauma. Cerebrovascular insufficiency is a secondary brain disorder characterized by a reduced cerebral blood supply, with carotid stenosis being one of its main causes.

1.3 EPIDEMIOLOGY

Stroke is the third leading cause of death after cardiovascular diseases and cancer. The World Health Organization, based on data from the 2016 Global Health Observatory (GHO), defines ischemic heart disease and stroke as the world's biggest killers,

causing 15.2 million deaths in 2016. These diseases have remained the leading causes of death globally for the past 15 years [3]. According to studies conducted by Amanda G. Thrift et al. on global stroke statistics obtained through reviews of previous case studies and analyses provided by the WHO, the incidence of stroke varies from 76 cases per 100,000 inhabitants per year in Australia to 119 per 100,000 inhabitants per year in New Zealand.[4] Of the 128 countries that have submitted data to the WHO, mortality is highest in Kazakhstan, Bulgaria, and Greece. Stroke incidence and mortality are both positively correlated with the population age group ≥ 65 years [4]. With particular attention to gender differences, a study conducted by Mozzafarian et al. highlights how men have a higher incidence of stroke than women (approximately 33%), who, having a longer life expectancy, have a lifetime risk of stroke between the ages of 55 and 75 of 20% versus 17% for men [5]. Within the European population of 715 million inhabitants, approximately 1.4 million strokes occur each year [6]. Stroke causes 1.1 million deaths per year in Europe, making it the second most common cause of death. Over half of subjects suffer from severe disabilities that place an enormous financial burden on healthcare systems, with annual costs exceeding 38 billion euros [7].

In Italy, 10-12% of deaths are due to stroke. In 2022 (latest available ISTAT mortality data), a total of 222,717 deaths occurred due to diseases of the circulatory system (97,225 in men and 125,492 in women)[8]. The age of death is between 65 and 84 years, and it mainly affects men. Globally, stroke was the third leading cause of death and the fourth leading cause of disability in 2021; it was estimated that, with an incidence of 11.9 million cases and a prevalence of 93.8 million cases, this pathology caused 7.25 million deaths, representing 5.6% of all years lost due to premature death or disability. Every year, approximately 186,000 strokes occur in Italy, of which approximately 80% are new episodes. The average age of onset is 74 years (72 for men and 76 for women). Ischemic stroke occurs in 67.3-82.6% of cases, intraparenchymal hemorrhage in 9.9-19.9% of cases, subarachnoid hemorrhage in 1.6-4% of cases, and a small percentage of cases remain undetermined. Thirty-day mortality is 18-33% and reaches 37-40% at one year. One year after the event, one-third of subjects die, one-third experience significant disability, and the remainder experience partial or complete functional recovery. The risk of recurrence within the first year is 10 times higher than in the general population. As we will discuss later, carotid stenosis is one of the main causes of ischemic stroke. Studies conducted by Faggioli G. et al. [9] show that the prevalence of age- and sex-related carotid stenosis is identical in both sexes in the 35-49 and 50-59 age groups; in the progressive age groups examined, the prevalence is higher in males than in females (Fig. 1). According to another study conducted by Rockman CB et al. [10] in 2013, the prevalence of carotid stenosis varies significantly based on ethnicity. Native American and Caucasian individuals have the highest prevalence of carotid stenosis, while African-American males and Asian females appear to have the lowest prevalence. Given the constant increase in life expectancy, it is clear that preventive strategies are needed to reduce the impact of the disease and its clinical implications, allowing the general population to reach advanced ages in the best conditions and with a dignified quality of life.

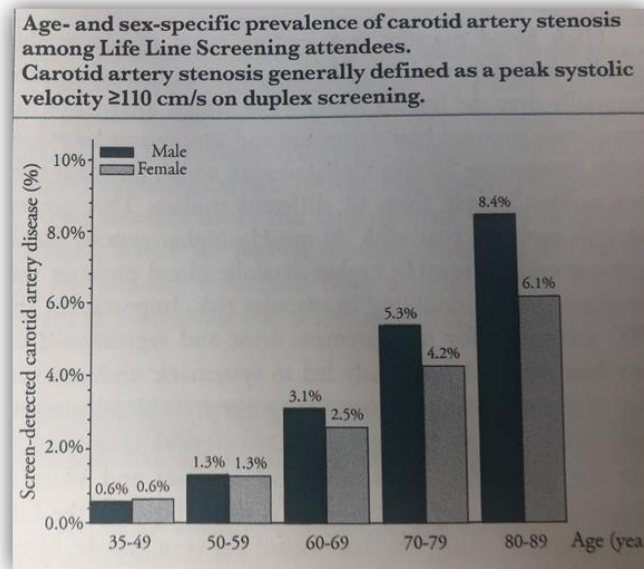


FIGURE 1 PREVALENCE OF CAROTID STENOSIS AGE-RELATED AND GENDER-RELATED (FROM FAGGIOLI ET AL.)[9]

1.4 ENDOVASCULAR TECHNIQUES

Angioplasty or PTA (Percutaneous Transluminal Angioplasty) and carotid stenting is a procedure that consists, generally through a percutaneous inguinal access under local anesthesia, of a balloon dilation (PTA) of the stenotic segment of the internal carotid artery and the insertion of a metal device (stent). The endovascular procedure involves the use of specific equipment, including a series of catheters, guide wires, introducers, PTA balloons, and stents.

The entry site. This represents the vessel from which the endovascular procedure begins and is distinct from the access site, which corresponds to the placement site of the guiding catheter or introducer, through which the treatment is performed. The two sites may coincide or belong to vascular segments that are even distant from each other. The choice of entry route is the result of a series of evaluations, including the possibility of having healthy vessels that allow for a safer procedure. The procedure begins with cannulation of a superficial and easily accessible artery:

- Transfemoral (TF) access: the right common femoral artery is the most commonly used entry site for CAS. The left common femoral artery is the second choice, especially in cases of steno- obstructive pathology of the right iliofemoral axis;
- Trans-cervical access: this site may be considered in cases of unfavorable aortic arch anatomy or in cases of calcifications, atherosclerosis, or tortuosity of the arch or its branches. The common carotid artery can be approached with a percutaneous puncture or direct puncture after surgical isolation, which can be safer although highly invasive;
- Trans-brachial and trans radial access. The first can be considered in cases of aortoiliac occlusion, a type III arch, or a bovine arch, or in the presence of other vessel tortuosity. The second has the same indications as the trans brachial approach and is more recently introduced.

The puncture is performed using the Seldinger technique: a needle is inserted into the vessel, a guidewire (the most commonly used in our center are the Jindo™ Cordis and the Hi-Torque Supra Core™ Abbott), and an introducer sheath equipped with a dilator is inserted (usually a short 8-F introducer sheath in our center).

Introducers, chosen based on the type of stent used and its dimensions, can be characterized by:

- length of shaft;
- caliber, expressed in French (usually 6 to 9);
- resistance to torsion and kinking;
- adaptability to curves.

The greater the adaptability to the anatomy of the vessel and the resistance of the introducer, the greater the efficacy, safety, and stability of the arterial access and the procedure.

Systemic heparinization. After positioning the introducer and before advancing the catheters into the arch, systemic anticoagulation should be performed with an intravenous bolus of approximately 100 IU/kg of sodium heparin, maintaining a clotting time no longer than 250-300 seconds.

Common carotid artery catheterization. Cannulation of the common carotid artery is a critical step in the CAS procedure. There are two most commonly used techniques:

- with a guiding catheter or a long introducer. Both these devices must be well irrigated with saline solution during the procedure, including through a continuous infusion connected to a pressure bag to prevent blood pooling (a potential cause of clots). In the guiding catheter technique (preferred at our center), a pre-formed 6F or 7F guiding catheter is advanced directly into the common carotid artery over a stiff guidewire. This technique has the advantage of avoiding repeated guidewire and catheter changes, reducing arterial manipulation and the risk of micro-embolisms in TSAs.
- The long introducer technique involves the use of a preformed 5F catheter that is used initially to cannulate the ostium of the common carotid artery. An exchange guidewire (usually 0.035 inch) is slid along the catheter and anchored in the external carotid artery. The exchange is performed with a long 6-Fr introducer, which is advanced with its dilator over the guidewire into the distal common carotid artery using a pull-and-push technique, below the bifurcation.

Angiography. Once the common carotid artery has been cannulated and the catheter has reached a stable position, angiography can be performed to identify the carotid bifurcation and the lesion to be treated. This is very useful for identifying the correct angle that allows a correct projection to be seen, minimizing overlap between the external and internal carotid arteries.

Cerebral protection device. To prevent the occurrence of embolization in the cerebral territory, a protection device should be used (Recommendation 8.1, SICVE Guidelines for the treatment of carotid disease). In the EVA-3S and CREST trials, the use of these devices significantly reduced the risk of embolization at 30 days. These studies consider brain protection mandatory during CAS. Commercially available devices will be discussed later in the project description.

Angioplasty, or PTA, involves the introduction of a catheter equipped with an inflatable balloon at its distal end. The guidewire is advanced until it reaches and passes the site of the stenotic lesion. An X-ray is performed to assess the lesion's position, then a balloon-filled catheter is coaxially inserted across the lesion and inflated. The characteristics of the catheter and balloon are unique and crucial to the success of the procedure.

The balloon catheter:

- must be robust but with minimal surface friction;
- must adapt to the position assumed by the guidewire along the arterial tree, easily crossing tortuous stenoses;
- must allow the passage of the guidewire inside it and of the contrast medium to be injected into the balloon. For this purpose, they have two lumens placed in parallel or coaxially.

The balloon, in turn, has some unique characteristics:

- its caliber must be 20-30% larger than that of the artery to be effective in resolving stenosis and, at the same time, minimize the risk of vessel dissection;
- the least "compliant" balloons are the safest because, when subjected to high pressure, they do not tend to over-distend. The non-distensibility of the balloon beyond the pre-established size therefore ensures an almost zero risk of over-distension of the arterial wall;
- finally, the balloon must have a good "memory", in other words it must return to the original caliber after inflation.

Stenting. This involves deploying a metal device, the stent, into the vessel to restore its patency. The characteristics of an ideal stent can be summarized as follows:

- excellent flexibility and maneuverability (let advancing along tortuous iliac vessels without altering their anatomy);
- low profile (shaped to produce the least possible friction upon contact with the arterial walls);
- easy and precise release system (balloon-expandable stents or sheath retraction in self-expanding stents: the former have the advantage of being able to be deployed with maximum precision, can over-dilate, and demonstrate high radial force, although they are less flexible and cannot be repositioned; self-expanding stents are very flexible and can be repositioned if the sheath has not been fully retracted, but are less precise in deployment);
- small diameter introduction system (avoids vascular trauma);
- high mechanical resistance (particularly radial) ;
- compliance similar with that of the vessel;
- secure anchoring (essential to avoid complications such as migration);

- excellent radioscopy visibility;
- available in different lengths and diameters.

There are different families of stents: tubular (laser-cut metal tube), modular (modules welded end to end), and truss. Their composition varies:

- steel has excellent biocompatibility and a modest elastic return (tendency to decrease in caliber after deflation of the balloon), but a relative thrombogenicity;
- the chromium-cobalt alloy allows for the production of a thinner stent, with good radiopacity and of sufficient resistance to crushing;
- ELGILOY, a cobalt-chromium-iron-nickel-molybdenum alloy, offers a combination unique with extremely high compressive strength and flexibility;
- nitinol (nickel-titanium alloy) is less thrombogenic than steel, but has a return significant elasticity which forces the stent to be over-sized;
- titanium has good biocompatibility, as does carbon. Less opaque stents have radiopaque markers at their ends.

Stents can also be divided into:

- tubular, which have as their main advantage their great radial strength, at the expense of limited flexibility. Their indications are calcified plaques or segments of the straight artery;
- modular, which have greater flexibility, at the expense of their radial strength. They are suitable for highly angulated areas and bifurcation zones but are less effective in calcified lesions.

Stents can be balloon-expandable, in which case they reach the desired diameter only after being dilated by the balloon catheter, or self-expandable. Nowadays, balloon-expandable stents were completely abandoned because their relative high rate of external compression, minimal conformability and insufficient lesion scaffolding, so they will not be analyzed forward [9]. The easily deployed self-expandable stents has some advantages due to their conformability and complete lesion coverage is feasible frequently with only one stent.[9]

There are two types, depending on the material they are made of:

- Elgiloy stents (Wallstent®), made of monofilaments of biomedical alloy DFT (Drawn-filled tubing) woven into a tubular mesh configuration that forms a spring. These endoprostheses are compressed in a carrier catheter and released by withdrawing the catheter's external sheath;
- shape-memory metal stents (nitinol or cobalt/platinum). These consist of a pre-cut lattice or tube that is cold-conditioned in its sheath. Upon release, these endoprostheses return to their pre-established diameter under the effect of body temperature.

There are some general types of self-expanding carotid stents: open and closed-cell, hybrid carotid stents, covered self-expandable, membranes stents, and more recently double-layer stents.

The stent design should provide vessel conformability, scaffolding, side branch preservation, visibility, and recoil control to minimize migration and foreshortening.[9]

The so-called first generation carotid stents are divided into two categories based on the design of their exposed cells: open-cell and closed-cell. The number and organization of the connecting bridges between the cells distinguish them. If the two adjacent rings are connected in every possible area, the stent is defined as closed-cell (see Fig. 2)

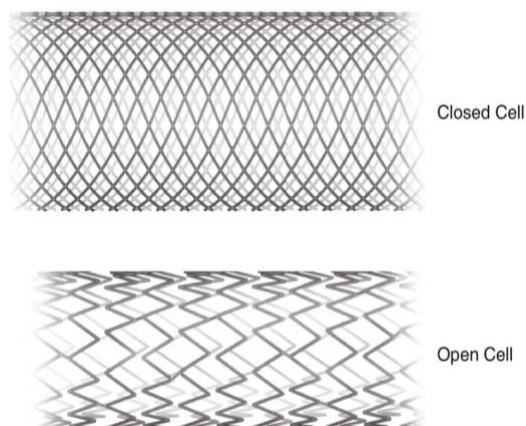


FIGURE 2 FIRST GENERATION CAROTID STENTS

Depending on the free area of the cell between the metal structures, closed-cell stents are characterized by free areas enclosed by rings connected at every possible point. Consequently, the size and shape of the cell area will influence the mechanical behavior of the device.

Care must be taken when placing closed-cell stents because, unlike open-cell stents, they undergo shortening after deployment and they tend to straighten the stented vessel. Hence the recommendation to place the closed-cell stent starting from its distal region, ensuring at least one centimeter away from the target lesion. Delayed straightening has been reported as a cause of restenosis, as when a closed-cell stent is placed on a tortuous lesion, it can cause straightening of the lesion and shortening of the vessel. This can sometimes lead to caudal migration of the stent, particularly when there is a significant difference in diameter between the internal and common carotid arteries, which more frequently shortens the common carotid artery, which is the larger vessel.

Open-cell stents, on the other hand, appear to cover a smaller surface area than closed-cell stents after deployment. These have the advantage of better following the anatomy of the vessel, reducing vessel straightening and preventing the development of dangerous kinks in tortuous lesions. Furthermore, the use of these stents reduces the risk of restenosis, but they do not offer the same level of embolization protection as closed-cell stents, resulting in an increase in peri-procedural

complications. Hybrid stents, with a central closed-cell portion and two peripheral open-cell portions, offer great flexibility and good resistance to microparticle penetration.

Covered stents are also available on the market, particularly self-expanding ones, which are used in cases of carotid aneurysms or dissections. The main limitations of these devices in the treatment of stenosing lesions are the high rate of restenosis.

In the last decade a new technology for carotid stents was introduced, gaining a great interest from a surgical-interventional perspective: dual-layer micromesh stent. These devices consist of a membrane composed of a micromesh of small pores placed on a metal structure that serves as the base of a self-expanding carotid stent. Two devices are on the market nowadays: Roadsaver (Terumo Corp., Tokyo, Japan) and CGuard (InspireMD Inc., Boston Maryland, USA) (fig.3).

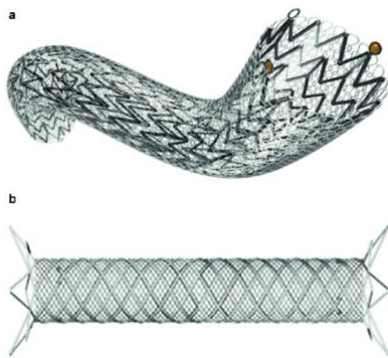


FIGURE 3 DUAL-LAYER MICROMESH STENTS (UPPER C-GUARD STENT, LOWER ROADSAYER STENT)

They show fundamental differences in:

- The stent nitinol frame construction (closed-cell in Roadsaver, open-cell in C-Guard);
- mesh material (nitinol in RoadSaver, polyethylene terephthalate (PTE) in C-Guard);
- mesh design (braided in Roadsaver, single fiber knitted in C-Guard),
- mesh position in relation to the stent frame (stent frame wrapped with mesh in the C-Guard stent, the mesh placed inside the frame in RoadSaver);
- inner layer pores diameter: 150–180 μm in C-Guard, 375 μm in Roadsaver;
- low-profile delivery system compatible with a 5.2 Fr catheter with a 0.014-inch guidewire in Roadsaver, 6Fr in C-Guard.

The strength of these new generation of stents lies in the extremely small pore size; these stents completely encase the plaque, theoretically minimizing the possibility of micro-embolic events both peri-procedurally and in the early and late postprocedural phases. More details will be discussed in a separated chapter.

Special aspects and intraoperative monitoring. As mentioned, cerebral protection devices are available on the market. Filter systems placed before the procedure are the most used today. The filter is contained in an external sheath, within which it is transported to the site and deployed. After the carotid stent is opened and its correct positioning is checked, the filter containing any residual trapped thrombi is retrieved and partially returned to the external sheath. The main advantage of these filters is their simplicity and the fact that they do not interrupt carotid blood flow during the procedure. The disadvantages are the

relative instability of the devices, which can shift during stent placement. Furthermore, there is no certainty about the complete adhesion of the filter to the arterial wall and, therefore, about its total efficiency and effectiveness. Sometimes, when a significant part of the fresh thrombus is trapped in the filter, carotid occlusion may occur. After implantation, in the initial stages, the stent is embedded in the wall along its entire length. Therefore, depressions form in the intima, which are quickly filled with thrombotic material, while the metal meshes become coated with a thin layer of fibrin. At the ostial regions, for example at the carotid bifurcation, one end of the stent may protrude from the arterial lumen, creating a thrombogenic area. Within a week of implantation, both surfaces are covered by endothelial cells. In the following weeks, a neointima forms, with the stent incorporating into the arterial wall. It is recommended to start dual antiplatelet therapy (DAPT) with aspirin (300 mg initially for a maximum of 14 days, followed by 75 mg daily, if not already being treated) taking aspirin and clopidogrel (75 mg daily) 3 days before CAS. Aspirin and clopidogrel should be continued for at least one month and, thereafter, it is recommended Clopidogrel alone. Most providers administer 5,000 IU of intravenous heparin before the procedure and 0.6–1.2 mg of atropine (or 0.6 mg of glycopyrrolate) before balloon inflation to prevent hypotension and bradycardia or asystole. A well-equipped angiography suite and/or operating room are required to perform a carotid stenting procedure.

Patients usually undergo carotid procedures under local anesthesia. Intra-operative continuous cardiac monitoring and careful measurement of systemic blood pressure are essential, as significant episodes of bradycardia and hypertension may occur. Level of consciousness and motor function must be regularly assessed. Monitoring the middle cerebral artery with transcranial Doppler ultrasound may also be useful, especially for visualizing micro-emboli. Additional neurological monitoring is provided by placing a sound-producing object in the patient's hand contralateral to the lesion being treated, which the patient squeezes at the operator's command. Once the lesion is reached, pre-dilation is only necessary in cases of very severe carotid stenosis (>95%); in this way, any wall friction during the passage of the stent through the stenosis is avoided and in-stent balloon angioplasty becomes easier to perform. When the angiographic control shows that it is in the correct position and the anti-emboli filter has already been introduced, the stent is released. After angioplasty and before filter removal, a final angiography should be performed to check vessel patency, verify proper stent placement, and assess cerebral vascularity. During this phase, spasm of the distal internal carotid artery is not uncommon. If significant spasm occurs, a small dose of nitroglycerin (50-100 ug) can be injected through the guiding catheter. At the end of the procedure, all material is removed and the access site must be closed. If the vessel is exposed, surgical suturing is performed. For percutaneous accesses, hemostasis is achieved through manual or mechanical compression, or with specific devices. Manual compression is applied for 10 to 20 minutes, applying a pressure slightly higher than systemic arterial pressure. A compression bandage is typically applied for 12 to 24 hours, with complete bed rest required

CHAPTER 2: REVIEW OF LITERATURE ON CAROTID ARTERY STENTING

2.1 CLINICAL STUDIES ON ENDOVASCULAR TREATMENT OF CAROTID STENOSIS

The CAVATAS (1992-1997, Carotid and Vertebral Artery transluminal Angioplasty Study) was the first multicenter RCT (n=504) to suggest that endovascular treatment of carotid artery stenosis may be non-inferior to TEA, although some results were difficult to interpret due to wide confidence intervals. Similar rates of periprocedural and long-term stroke, death, and restenosis were observed in the two groups, although a greater number of nerve damage, wound hematomas, and neck hematomas occurred in the TEA group. Furthermore, in the TEA group, endovascular, patients undergoing stenting (n=50) had a significantly lower restenosis rate than those undergoing balloon PTA (n=145)[11].

The SAPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial was the only one to compare CAS to TEA in patients at high risk for surgery (defined as having clinically manifest heart disease, severe bronchopathy, contralateral carotid occlusion or contralateral laryngeal paralysis, previous radical neck surgery or neck radiation therapy, recurrent stenosis after TEA, and age over 80 years). More than 70% of participants (n=334) in the trial had asymptomatic stenosis. It reported non-inferiority of CAS with respect to death, periprocedural myocardial infarction, and stroke, and with respect to post-procedural death and stroke, although the number of these events was significantly higher. No statistically significant differences were observed in terms of death, stroke, death or myocardial infarction, ipsilateral stroke between day 31 and year 3, and restenosis in the two groups [12].

Among trials dedicated to patients with symptomatic stenosis, the ICSS (2001-2008, International Carotid Stenting Study) was the largest RCT comparing CAS with TEA (n=1713). [13] The incidence of stroke/death/ myocardial infarction within 120 days of treatment was higher in CAS, as were the 5-year stroke rates. The combined outcomes of procedure-related stroke/death or ipsilateral stroke during follow-up were also more frequent with CAS; in addition, more cranial nerve damage and hematomas occurred with TEA. Long-term rates of restenosis or occlusion did not differ between the two groups.

The EVA-3S trial (2000-2005, Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis), A multicenter non-inferiority RCT (n=1200) with a median follow-up of 7.1 years saw poorer results.[14] The very high rates of periprocedural stroke and death led to the trial's premature termination. This also meant that 80% statistical power was not reached, making the data difficult to interpret. Although the 5-year rates of periprocedural stroke and death and non-intraprocedural ipsilateral stroke were significantly higher in CAS, the 10-year outcomes were not significantly different. The high rates of periprocedural stroke and death with CAS explained this, with similar postprocedural stroke rates between the two groups. No significant difference was observed in restenosis rates.

The SPACE trial (2001-2006, Stent-Protected Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy) showed similar results (n=1200).[15] Non-inferiority CAS has not been demonstrated with respect to periprocedural

death/periprocedural stroke. The 2-year rates of ipsilateral stroke and 2-year periprocedural death and stroke were similar between the 2 groups. Restenosis was more frequent with CAS.

The CREST (2000-2008 Carotid Revascularization Endarterectomy vs. Stenting Trial) randomized 2,502 asymptomatic and symptomatic patients to CAS with a cerebral protection device or TEA at standard surgical risk.[16] It had a median follow-up of 2.5 years and showed no significant differences in death, stroke, or myocardial infarction. Importantly, in the second half of the study, the stroke rate in the CAS arm showed a significant reduction, which was not observed in the CEA arm, suggesting a "learning curve" for the endovascular arm. Finally, in CREST, there was an association between the presence of periprocedural myocardial infarction, more common in the TEA arm and long-term mortality.

The ACST-2 (2008-2020, Asymptomatic Carotid Surgery Trial), which was the most large RCT ever conducted comparing CAS and TEA enrolled 3,625 patients with asymptomatic carotid stenosis, with an indication for carotid revascularization determined by a multidisciplinary team, and eligible for both procedures.[17] This study showed no difference in the main 30-day outcome of death, myocardial infarction, or stroke, with a rate of 3.9% in the CAS arm and 3.2% in the TEA arm ($p = 0.26$). An excess of non-disabling stroke was observed in the CAS arm (2.7% vs. 1.6%, $p = 0.03$), driven by an increase in strokes with a modified disability rating scale of 0, i.e., without stroke symptoms at 6 months. Estimated 5-year Kaplan-Meier curves reveal no difference in any non-procedure-related stroke between CAS and CEA, as well as in non-procedure-related fatal or disabling strokes. Remarkably, there were no differences in the 5-year stroke rate even in patients over 70 years of age.[18]

The Stent-Protected Angioplasty vs Carotid Endarterectomy (SPACE)-2 RCT reported its 5-year results.[9] SPACE-2 was a multicenter ($n = 36$) RCT enrolling patients aged 50 to 85 years with $\geq 70\%$ asymptomatic carotid stenosis (AsxCS) (513 patients in the period 2009-2019). 203 (40%) were allocated to CEA vs BMT, 197 (38%) to trans-femoral (TF)-CAS Vs BMT, and 113 (22%) to BMT alone.[9] After a median follow-up of 59.9 months (interquartile range, 46.6-60.0 months), the cumulative incidence of any stroke or death from any cause within 30 days and any ipsilateral ischemic stroke within 5 years was 2.5% for CEA vs BMT, 4.4% for TF-CAS Vs BMT and 3.1% with BMT alone (hazard ratio [HR] for CEA vs BMT vs BMT alone: 0.93; 95% CI, 0.22-3.91; $p = 0.93$; HR for TF-CAS vs BMT vs BMT alone: 1.55; 95% CI, 0.41-5.85; $p = 0.52$).[19] It was concluded that CEA vs BMT or TF-CAS p BMT are not superior to BMT alone, but it was advised that the results should be interpreted with caution owing to the small sample size (the study was halted prematurely owing to slow patient enrollment). [20]

The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trials (CREST-2) results recently published [2] have spread new enthusiasm to endovascular approach in carotid artery stenting. Study design was two parallel, observer-blinded clinical trials that enrolled patients with high-grade ($\geq 70\%$) asymptomatic carotid stenosis across 155 centers in five countries [2]: a stenting trial, in which patients were randomly assigned to receive either intensive medical management alone (medical-therapy group) or carotid-artery stenting plus intensive medical management (stenting group) and an endarterectomy trial, in which patients were randomly assigned to receive either intensive medical management alone (medical-therapy group) or endarterectomy plus intensive medical management (endarterectomy group).[2] Patient eligibility and trial assignment were established by the trial site, guided by differences in eligibility criteria specific to carotid-artery stenting or carotid endarterectomy. [2] The primary outcome was a composite of any stroke or death, assessed from

randomization to 44 days, or ipsilateral ischemic stroke, assessed during the remaining follow-up period up to 4 years. [2] The stenting trial showed the addition of transfemoral carotid-artery stenting to intensive medical management led to a significantly lower risk of the primary composite outcome (periprocedural stroke or death or postprocedural ipsilateral stroke within 4 years) as compared with intensive medical management alone (2.8% vs. 6.0%). [2] The absolute risk difference of 3.2 percentage points was significant, corresponding to a number needed to treat of 31 to prevent one primary-outcome event. [2] Carotid endarterectomy plus intensive medical management did not provide a significant benefit as compared with intensive medical management alone. [2] An ongoing long-term post-trial follow-up study, as was done in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) trial, [21] is evaluating longer-term outcomes for the comparisons of carotid-artery stenting and carotid endarterectomy with intensive medical management. [22] The identification of features of carotid atherosclerosis that may benefit from revascularization warrants future research. [23] This trial has several limitations: first of all, although stroke adjudicators were unaware of the treatment assignments, patients and treating physicians were not; second, various changes in medical-therapy practices occurred during the trials that could lower stroke rates and negate any additional benefit of revascularization; third, revascularization was performed only by well-trained and certified high-volume operators, so the results in CREST-2 may not reflect practice more broadly; fourth, trans-carotid artery revascularization came into frequent use after approximately one half the patients had undergone randomization, and thus this approach could not be incorporated in the trial.

In the last few years, trans-carotid artery revascularization (TCAR) has emerged as an alternative hybrid/endovascular option to trans-femoral(TF)-CAS. Several nonrandomized studies have reported that TCAR is associated with lower stroke and death rates compared with TF-CAS, whereas it is associated with similar stroke and death rates compared with CEA [24-25-26-27]. An analysis of data from the Vascular Quality Initiative registry between September 2016 and June 2021 on patients undergoing CEA (n = 82,737), TF-CAS (n = 14,595), and TCAR (n = 14,595) across 662 centers demonstrated that the perioperative rate of stroke or death for patients with AsxCS was 1.1% for CEA, 1.2% for TCAR, and 1.8% for TF-CAS (for TF-CAS vs CEA/TCAR; $P < .001$), whereas the 1-year stroke and death rates were 3.8%, 4.9% and 6.6%, for patients with AsxCS undergoing CEA, TCAR, and TF-CAS, respectively (for TF-CAS vs CEA/TCAR; $P < .001$). [28] A limitation of TCAR is that it has never been compared with CEA, TF-CAS, or BMT in any RCT.

2.2 CLINICAL STUDIES ON GENDER DISPARITIES IN CAROTID ARTERY TREATMENT

The Asymptomatic Carotid Atherosclerosis Study (ACAS) was the first large, randomized trial to compare medical versus surgical treatment for asymptomatic carotid stenosis greater than 60% (measured by the NASCET method). [29] In that study, women had a higher rate of perioperative events (3.6% vs. 1.7% for men) during CEA. Among patients with moderate stenosis, in the NASCET (North American Symptomatic Carotid Endarterectomy Trial), the number needed to treat with CEA to prevent one ipsilateral stroke and one disabling Stroke were 12 and 16 for men, respectively. [30] The corresponding numbers for women were 67 and 125, respectively, potentially suggesting a lower long-term benefit of surgery for women.

The ACST-1 (Asymptomatic Carotid Surgery Trial) study produced similar results, with men achieving a greater absolute risk reduction at 5 years (8.21% vs. 4.08%) than women. [31] Women in the International Carotid Stenting Study (ICSS) trial had a higher 120-day event rate for CEA (7.6% vs. 4.2%) but a lower rate for CAS (8.0% vs. 8.7%).[13] A diametrically opposite situation is configured in the CREST study (Carotid Revascularization Endarterectomy vs Stenting Trial): a higher rate of periprocedural events lower for women undergoing CEA (3.8%) than for men (4.9%) but higher in CAS (6.8% vs. 4.3%).[32] With potentially higher perioperative event rates, these data raise the question of how much women actually benefit from the procedure. Therefore, further data are needed to confirm whether this differential risk should be taken into account in treatment decisions for carotid disease in women.

Gender clearly plays an important role in cardiovascular disease. A 2009 systematic review of epidemiological studies by Appelros et al. found that the incidence and prevalence rates of stroke were 33% and 41% higher in men than in women, respectively.[33] When strokes did occur, however, they tended to be more severe in women. The specific factors that would lead to differential gender-specific perioperative and long-term outcomes after carotid endarterectomy remain unclear.

Several factors, including vessel diameter, plaque morphology, the influence of sex hormones, different sensitivity to antiplatelet therapy, restenosis rate, and thromboembolic potential, have been proposed as causes of possible gender-specific outcomes. Greater embolic potential and relatively stable plaque morphology in women are the best-described factors that could influence the difference in outcomes between men and women. However, the overall evidence for gender-specific outcome differences in the literature is rather limited.[34] The analysis conducted by Giannopoulos et al. published in 2013 reviewed the available literature using a combined search of the terms: age, gender, sex, carotid artery stenosis, carotid stenting (CAS), and carotid endarterectomy (CEA).[35] From the findings to that point, it was evident that postoperative stroke and mortality rates increased with age after any carotid revascularization procedure (CEA or CAS), especially in patients over 75 years of age. [35] Specifically, older patients undergoing CAS had a doubled risk of stroke and death compared to patients undergoing CEA, while CEA provided greater benefits in patients over 70 years of age with symptomatic carotid stenosis.[35] Male patients with symptomatic or asymptomatic carotid stenosis had lower stroke/mortality rates and benefited more from CEA than females.[35] There were no gender differences in the risk of periprocedural stroke or death after CAS, although CEA appeared to pose lower periprocedural risks than CAS in patients >70 years of age. [35] The periprocedural risk of CEA was lower in men than in women, while there were no gender differences in the periprocedural risk of CAS.[35] In light of the above considerations, therefore, a review of published data available in the literature was conducted on the potential effects of age and gender stratification in symptomatic and asymptomatic patients undergoing revascularization procedures, CAS, or CEA.[36] Data collected through the MEDLINE and EMBASE systems using a combination of the aforementioned terms, with particular attention to gender disparities, showed that male patients with symptomatic or asymptomatic stenosis had lower stroke/mortality rates and benefited more from the surgical procedure (CEA), unlike females. In patients with carotid stenosis undergoing CAS, no gender differences were observed.[36] However, in the CREST trial, women undergoing CAS had an increased risk of periprocedural complications compared to women undergoing CEA.[36] These findings were not confirmed in the larger meta-analysis by Touze et al. in 2009 on the combined databases of the ICSS and CREST trials.[37]

Many epidemiological studies and randomized trials would agree in defining the male sex as having the highest incidence and prevalence of stroke, 33 and 41%, respectively, especially at a younger age (on average 4.3 years earlier than females). [33,38,39,40 ,41,42] However, women are more severely affected by stroke than men and have a lower 30-day mortality rate

than men.[33] Furthermore, women would have a 24% higher survival rate than men, thus being more exposed to the risk of a cerebrovascular event according to the work of Appellos et al. in 2009.[33] Furthermore, according to the work of Turtzo et al. in 2008, women with ischemic stroke would undergo surgical revascularization procedures less frequently than men, since the risk/benefit ratio of surgical treatment in females would still be a topic of debate.[39] It should also be noted that the percentage of female patients undergoing CEA has remained constant over the last 20 years, resulting significantly lower than the percentage of men.[40]

Other potential explanations found in the available literature for gender disparities in benefit achieved with CEA could be attributed to:

- higher rates of carotid artery stenosis and lower plaque burden for the same degree of carotid stenosis in women compared with men;
- higher surgical risk in women, since the female sex would be characterized by both smaller body dimensions and smaller ICA dimensions and, therefore, the technical difficulties of CEA in female patients would be higher than in male patients;
- higher postoperative complications of CEA in women, such as the risk of postoperative microembolization in the first hour after CEA monitored with TCD ultrasound, would be significantly higher in women;
- lower cerebrovascular reserve in women, such as cerebrovascular reactivity after hypercapnia, which would be more impaired in postmenopausal women than in men of the same age;
- higher risk of post-procedural complications (carotid restenosis and ipsilateral stroke) after CEA or CAS greater in females than in males. [41,42,43,44,45,46,47,48]

Some limitations in interpreting the results of this review should be considered. Among these, the small number of women and patients over 75 years of age who were enrolled in the carotid revascularization clinical trials and the lack of reference to surgical expertise could weaken the results of the reported subgroup analyses.[49][50] Finally, it should be highlighted that, in recent years, the documented risk of ipsilateral ischemic stroke in patients with asymptomatic carotid stenosis of a certain degree has been significantly reduced thanks to medical interventions including the use of statins and antihypertensive drugs. In a 2010 study conducted in the United Kingdom, the average annual risk of stroke and/or ipsilateral TIA in patients with asymptomatic stenosis $\geq 50\%$ undergoing intensive medical treatment was found to be rather low (0.34% for ipsilateral ischemic stroke). [51] These results would be in agreement with two other reports, one Australian (3-year risk of ipsilateral ischemic stroke in patients with asymptomatic carotid stenosis $\geq 60\%$: 1%) [52] and a Dutch one (5-year risk of cerebral infarction in patients with asymptomatic carotid stenosis $\geq 50\%$: 2.2%). [53] A study conducted on 106,568 patients from the American College of Surgeons National Surgical Quality Improvement Program database, 39.9% of whom were women, who underwent carotid revascularization (TEA or CAS) between 2005 and 2017, showed statistically significant differences in multivariate regression for the risk of cerebrovascular accidents, bleeding and urinary tract infections for women (undergoing TEA or CAS) compared to men 30 days after surgery.[54]

Data from The Society for Vascular Surgery (SVS) Vascular Registry (VR) were used to determine the effect of gender on perioperative (30-day) outcomes in patients undergoing carotid endarterectomy (CEA) and carotid stenting (CAS)

procedures.[54] The VR was one of the largest published databases of carotid revascularization procedures in the United States. [46] The primary outcome was a composite of the incidence of death, stroke, or myocardial infarction. [54] The analysis of 30-day outcomes was based only on those patients who had a follow-up of at least 30 days (>16 days) or who had an endpoint (death, stroke, or myocardial infarction) ≤ 30 days after treatment. [54] For the purposes of this study, the analysis was limited to patients treated for carotid disease caused by atherosclerosis, radiation, and restenosis. [54] This resulted in the exclusion of 454 patients treated for alternative etiologies (e.g., dissection, fibromuscular dysplasia, and trauma). There were 9,865 patients with 30-day follow-up data, with 40.6% women (n = 4,008) and 59.4% men (n = 5,857). [54] For CEA (65.8%; n = 6,492), 41.3% were women (n = 2,678) and 58.7% were men (n = 3,814). For CAS (34.2%; n = 3,373), 39.4% were women (n = 1,330) and 60.6% were men (n = 2,043). [46] Men and women had a similar ethnic and age profile. [54] Women were more likely to be treated for restenosis (10.2% vs. 7.8%) and less likely for radiation-induced disease (0.9% vs. 2.3%). [54] Men were more likely to be treated for symptomatic disease (41.6% vs. 38.6%).[54] In patients undergoing CEA, there was no statistically significant difference in 30-day outcomes. [54] The primary endpoint was nearly identical (4.07% female and 4.06% male), as were the individual endpoints of mortality, stroke, or myocardial infarction. [54] Asymptomatic patients undergoing CEA had the lowest event rates, with the composite rate of death/stroke/myocardial infarction being 3.03% in women and 3.19% in men. [54] The rate was higher in symptomatic patients, with the primary endpoint occurring in 5.94% of women and 5.42% of men. [54] Even after risk adjustment, no difference was detected (OR 1.15; 95% CI, 0.89 to 1.48; p = 0.2958) between women and men undergoing CEA. [54] In CAS patients, there was still no statistically significant difference in outcomes between the two genders. [54] The composite rate of death/stroke/myocardial infarction was 6.69% in women and 6.80% in men, higher than the rate of 4% in patients undergoing CEA. [54] In asymptomatic patients, the event rate was higher for women (5.79% vs. 4.55%; p = 0.2353). [54] There was also a higher rate of the primary endpoint in symptomatic men (9.42% vs. 7.84%; p = 0.3088) compared to women. [54] In the end, none of these reached statistical significance. [54] After risk adjustment, no difference was observed between women and men (OR 0.91; 95% CI, 0.68 to 1.21; p = 0.5115).[46]

In the last years, Casana et al [55] showed in a single-center retrospective study for peri-procedural outcomes, women undergoing carotid artery stenting had a higher risk of moderate (50–70%) restenosis (6 women, 2.9%, vs. 3 men, 1.0%) in a population of 523 consecutive CAS.[55] On the other hand, Desantis et al. [56] showed in a retrospective single center study (438 asymptomatic carotid stenosis treated) gender variable does not influence outcomes of CAS in asymptomatic patients at short- and long-term follow-up, although females show a worst incidence of periprocedural major strokes. [56] Fornelli et al [57] published a retrospective monocentric study on 568 patients (366 males and 202 females), submitted to CAS, between January 2000 and December 2019. [49] In this study male patients were more likely to be octogenarians, clinical history of coronary artery disease, and smokers, while diabetes was more frequent in female patients.[57] Results showed no differences in immediate and long-term CAS outcomes between gender, even though was observed a slight majority of women dying on the long term (9,2%, males 34,9% vs. females 47%, P= 0,0048; OR 0,65 CI95% :0,42–0,85) [57] Recently in Japan, the outcomes of women and men were compared using the data from nationwide retrospective registry between 2015 and 2019. [58] The primary outcome was the incidence of ischemic stroke and all-cause death. [50] Secondary outcomes included the incidence of ischemic stroke, all-cause death, acute occlusion, and acute myocardial infarction. In total, 9792 patients (1330 women, 8862 men; mean age, 73.8 vs 73.5 years, p =0.17) were analyzed.[58] In this large national retrospective study CAS

for carotid artery stenosis suggests that there was no significant gender differences in the incidence of ischemic stroke and all-cause death at 30 days. [58] However, women showed higher rate of all-cause death. [58]

In a recent systematic review a total of 84,336 and 139,848 CAS procedures performed in female and male patients, respectively. [59] Among studies that did not stratify outcome by symptomatology, there was no difference in the 30-day outcomes between genders for patients undergoing CAS. [59] Asymptomatic patients undergoing CAS demonstrated similar incident rates across perioperative myocardial infarctions (MI)s (female: 0% to 5.9% v male: 0.28% to 3.3%), CVAs (female: 0.5% to 4.1% v male: 0.4% to 6.2%), and long-term mortality outcomes (female: 0% to 1.75% v male: 0.2% to 1.5%). [59] Symptomatic patients undergoing CAS similarly reported higher incidences of perioperative MIs (female: 0.3% to 7.1% v male: 0% to 5.5%), CVAs (female: 0% to 9.9% v male: 0% to 7.6%), and long-term mortality outcomes (female: 0.6% to 7.1% v male: 0.5% to 8.2%). [59] Studies regarding gender-stratified outcomes after carotid stenting were more limited and included both transfemoral and trans-carotid approaches. [59] Only two studies in the literature reported sex-based outcomes after TCAR. [51] Interestingly, the same studies previously noted that identified sex-related differences in outcomes after CEA also reported a difference in gender-related outcomes after carotid stenting. [59] An increased perioperative neurologic event rate for female patients compared with male patients was noted by Mayor et al. [60] in their symptomatic cohort and by Dansey et al. [61] in their asymptomatic cohort. Although the trend across most studies was an increased incidence of perioperative MI in female patients, only Bisdas et al. [62] reported a statistically significant difference; female patients had a higher rate than male patients (0.96% v 0.28%; $P = .01$). [59] With respect to late outcomes, Fornelli et al. [57] reported a difference in late mortality in their cohort of patients undergoing transfemoral stenting, which was significantly worse in female patients. [59] It is important to note that this study did not stratify patients by symptomatic status. [59] The remaining studies on late follow-up showed no difference in outcomes when stratified by gender. [59] More adequately powered studies are needed to understand the etiologies of these gender-based differences in outcomes and help us provide better patient-centered care. [59] In spite of the currently published outcomes in female patients, appropriately selected patients should be offered a carotid intervention. [59]

CHAPTER 3: THE ROLE OF INFLAMMATION AND THE RESEARCH OF A BIOMARKER

Atherosclerosis is not simply a disease caused by the accumulation of cholesterol and macrophages, because it is characterized by a pathogenesis in which inflammation plays a crucial role. [63] Inflammatory and immune mechanisms influence the development and progression of atherosclerotic plaques [64][65][66]. Patients with atherosclerotic lesions in multiple arterial locations, including the extracranial carotid artery, exhibit elevated plasma levels of various markers of systemic inflammation. Both ischemic and hemorrhagic stroke patients' short-term prognosis and in-hospital mortality have been predicted by inflammatory markers [67][68][69][70][71][72]

There are many laboratory indices of inflammation, such as the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), which have been the subject of numerous studies [73][74][75][76][77][78][79][80][81], especially in the oncology field, and which are correlated with worse outcomes in patients with acute myocardial infarction and carotid stenosis.[82] A prognostic index recently studied has been the albumin/neutrophil ratio, which appears to be correlated with the risk of restenosis after carotid PTA stenting.[83] Other biomarkers such as the monocyte/lymphocyte ratio (MLR)[84] systemic inflammation index (SII)[85], systemic immune response index (SIRI)[86] and aggregated inflammation response index (AISI)[87] could be assessed similarly to the study by Niculescu et al.[88]. [89]

Proatherosclerotic factors, such as hyperlipidemia and oxidative damage, can trigger systemic inflammation.[90] This inflammation is currently regarded as the core mechanism of atherosclerotic formation.[73] It leads to release of pro-inflammatory cytokines, resulting in an increased neutrophil count.[90] Concurrently, this inflammatory state is also associated with a low lymphocyte count.[72] NLR also showed potential in predicting ISR in patients undergoing non-coronary stenting.[72] Higher NLR faced 1.7 times the fold of ISR occurrence.[72] Linear dose response relationship demonstrated 40% chance of having ISR per increase in one-unit NLR.[64] The present result showed NLR possesses favorable predictive value.[72] Similar to coronary stenting, inflammation is also a critical factor in the development of ISR in non-coronary stenting including peripheral and carotid arteries, involving early-stage neointimal hyperplasia following arterial injury, where neutrophils play a critical role through the release of myeloperoxidase, matrix metalloproteinase [72] , and free radicals, while certain lymphocyte subsets reduce inflammation.[72] Following arterial stenting, platelet and fibrin accumulate around the stent, sparking acute inflammation initially, which transitions to a granulation tissue response involving neovascularization, smooth muscle cell migration, proliferation, and the gradual replacement of acute inflammatory cells with chronic ones [89]. In addition, patients with coronary artery disease and high NLR have increased inflammation and a higher risk of acute coronary events. Kurniawan et al. [64] in a recent meta-analysis found high NLR is associated with a higher risk of all-cause mortality, major adverse limb events, and major adverse cardiovascular events among patients with peripheral artery disease.[72]

Recent evidence suggests that the inflammatory response following vascular interventions differs by procedure type.[91] Scalise et al.[89] found that CEA elicits a stronger inflammatory reaction than CAS, as evidenced by elevated levels of inflammatory biomarkers post-surgery.[83] High levels of C-reactive protein and fibrinogen were identified as predictors of

early restenosis, emphasizing the critical role of inflammation in vascular healing and ISR.[91] Patients with ISR and a high NLR are more likely to have soft plaque, which facilitates guide wire passage but is prone to rupture or dislodgement. [91] Davies et al. [92] found that soft plaque, combined with elevated high-sensitivity C-reactive protein, is a key predictor of ISR. [91] The possible underlying mechanism of positive relationship between NLR and ISR may be explained as follows. In-stent restenosis has been attributed to neointimal hyperplasia in the early stage after the procedure.[93] After acute mechanical arterial injuries, platelet and fibrin deposit at the injured site and then leukocytes, including neutrophil, are recruited to the site through leucocyte–platelet interactions.[94] Over time, effects of cytokines and growth factors from platelets, leukocytes, and vascular smooth muscle cell ultimately result in neointimal hyperplasia.[95] Neutrophils aggravate the inflammatory response and plays a critical role in the neointimal hyperplasia through the release of myeloperoxidase,[96] matrix metalloproteinase[97][98] and oxygen-derived free radicals.[99] In contrast, certain subsets of lymphocytes were shown to dampen inflammation.[100] Therefore, an elevated NLR may represent an increased inflammatory status that promotes ISR development. Considering some patients received statin therapy in the study, NLR was still a predictor of ISR after CAS for asymptomatic lesions despite the anti-inflammatory effect of statins.[101] Previous studies indicated that carotid plaques from patients with stroke or TIA contain increased levels of inflammatory mediators than those from asymptomatic patients[102]. Furthermore, plaque composition has been related to ISR after endarterectomy.[103] In Dai Z et al. [72] study was not evident a significant relationship between NLR and ISR after CAS for symptomatic lesions. This may be explained as follows: firstly, CAS of lipid-rich plaques is believed to cause less vascular trauma than fibrous plaques because of lower stent release pressure.[104] This results in decreased infiltration of inflammatory cell, thereby less influence of preprocedural systematic inflammatory state. [72] Secondly, the local inflammatory responses after CAS result from both local and infiltrative inflammatory cells.[97] It is believed that patients with many inflammatory cells in their plaques have a large amount of leukocytes in the vessel wall that remain in situ after CAS.[105] Therefore, symptomatic lesions receive less influence from preprocedural inflammatory state in comparison with asymptomatic lesions.[105] In addition, this study indicated that smoking and residual stenosis were significantly associated with ISR after CAS for asymptomatic stenosis.[105] Residual stenosis is a risk factor for restenosis; this is in conflict with the opinion that a perfect angiographic result after CAS is not necessary.[106] Because high post-dilation pressures result in increasing risk of embolization and neointimal proliferation,[107] pre-dilation may be an effective measure to relieve the residual stenosis.[80]

The SII is considered as a modified powerful combination of NLR and PLR. [82] Preliminary studies in oncology seem to suggest that high values correlate with an unfavorable prognosis. [108][109][110][111][112] In the cardiovascular field, the study of this new biomarker is attracting growing interest and appears to correlate with adverse events in patients with heart failure and obstructive coronary artery disease. [113]

A 2021 retrospective single-center study by Keskin et al. [82] examined the prognostic value of SII in CAS patients regarding in-hospital 5-year outcomes. 732 patients were included in this study: CAS procedures were all performed under local anesthesia via femoral access, using the “guiding-catheter technique”, distal embolic protection with a vascular filter was used in all patients during CAS procedures, self- expanding stents were used for the management of carotid artery stenosis, the post-procedural anti-platelet therapy was continued (clopidogrel for the first 4-6 weeks in asymptomatic patients, 3 months in symptomatic patients and aspirin indefinitely in all patients) and high-dose statin (80 mg atorvastatin or 40 mg rosuvastatin) were prescribed the day before and after discharge for all patients unless contraindicated.[82] Baseline characteristics were

compared among the patients by admission SII level and categorized accordingly: T1, T2 and T3.[82] Primary endpoints were: all-cause mortality, stroke, MACE (myocardial infarction, TIA, stroke and death).[82] During hospitalization, major stroke, ipsilateral stroke, MI, death and MACE rates were significantly higher in high SII level (T3) compared to SII levels (T1 and 2).[74] ROC analysis showed that the best cut-off value of the SII to predict the in-hospital mortality was 822 with 78% sensitivity and 68% specificity (AUC: 0.73; 95% CI:0.63-0.83; $p < 0.001$). [82]In long-term out- comes, ipsilateral stroke, major stroke, transient ischemic attack, death, and MACE were significantly higher in patients with higher SII level (T3).[82] The 5-year Kaplan-Meier overall survival for T1, T2, and T3 were 97.5%, 96.7% and 86.0% respectively. [82] These significant relationships were also evident even after adjustment for all confounders. In-hospital mortality and MACE rates were similar between T1 and T2 groups.[82] Patients with higher SII level (T3) had higher 3-year mortality that had 5.3-times higher mortality rates (95% CI: 1.8 16.0) than lower SII level (T1) which had the lower rates and used as the reference. [82] The 5-year MACE was also higher in patients with higher SII (T3) that was 6.1-times higher (95% CI: 3.0 12.4) than lower SII (T1).[82]

TABLE I IN-HOSPITAL AND 5-YEARS OUTCOMES FROM KESKIN ET AL. STUDY [74]

In-hospital outcomes	T1 (n=244)	T2 (n=244)	T3 (n=244)	P value
Ipsilateral stroke	3 (1.2)	4 (1.6)	11 (4.5)	0.039
Major stroke	2 (0.8)	2 (0.8)	8 (3.3)	0.047
Transient ischemic attack	6 (2.5)	9 (3.7)	20 (8.2)	0.008
Myocardial infarction	3 (1.2)	6 (2.5)	14 (5.7)	0.013
Death	2 (0.8)	2 (0.8)	15 (6.1)	<0.001
Major adverse cardiovascular events	12 (4.9)	14 (5.7)	39 (16.0)	<0.001
Long-term outcomes	T1 (n=242)	T2 (n=242)	T3 (n=229)	
Ipsilateral stroke	2 (0.8)	4 (1.7)	20 (8.7)	<0.001
Major stroke	2 (0.8)	2 (0.8)	16 (7.0)	<0.001
Transient ischemic attack	5 (2.1)	6 (2.5)	18 (7.9)	0.002
Myocardial infarction	3 (1.2)	4 (1.7)	16 (7.0)	<0.001
Death	4 (1.7)	6 (2.5)	19 (8.3)	<0.001
Major adverse cardiovascular events	10 (4.1)	17 (7.0)	48 (21.0)	<0.001

These significant relationships were also evident after adjustment for all confounders.[82] Long-term mortality and MACE rates were similar between T1 and T2 groups.[74] The results of the present study suggest that significant prognostic information can be obtained from routine blood test results in patients undergoing CAS. [82] This study showed that high SII values at admission was independently associated with in-hospital and long-term mortality and MACE in CAS patients. [82] SII improved the risk prediction of major cardiovascular events than traditional risk factors in patients with carotid artery stenosis who underwent CAS. [82] This index may be used as an easy and practical indicator to identify high-risk patients undergoing CAS.[82]

Morikawa at al [114] in a single center study aimed to investigate whether SII can accurately predict the short- and long-term prognoses in patients who underwent CAS compared to that with C-reactive protein (CRP). 129 patients who underwent CAS were categorized into tertiles based on their SII levels. In this study the inclusion criteria were <50% carotid artery stenosis in symptomatic patients or <80% stenosis in asymptomatic patients [114]. A symptomatic lesion was defined as the presence of a transient ischemic attack or ischemic stroke within the preceding 6 months [114]. The exclusion criteria were as follows: (1) patients aged >85 years; (2) those with systemic inflammatory disease; (3) those with malignancy; (4) those with liver

failure; and/or (5) those with end-stage renal failure.[114] This study's primary endpoint was the incidence of long-term (from discharge to 5-year follow-up) MACCE, which included all-cause mortality, stroke, and myocardial infarction. [114] The secondary endpoints were the incidence of stroke both in-hospital and during the long-term follow-up, and all-cause death. [114] The in-hospital stroke rate tended to increase with a rise in SII ($P=0.13$). [114] Over the 5-year follow-up period, the Kaplan–Meier overall incidence of MACCE was 9.3%, 16.3%, and 39.5% in the lowest to highest tertiles, respectively (log-rank trend test, $P<0.001$). [114] The rates of stroke and MACCE during the long-term follow-up were significantly higher with increasing SII. [114] Cox regression analysis showed that the highest tertile of SII (>647) was a predictor of the incidence of long-term stroke (hazard ratio (HR), 21.3; 95% confidence interval (CI), 2.41–188; $P=0.006$) and MACCE (HR, 3.98; 95% CI, 1.80–8.81; $P<0.001$). [114] However, after adjusting for both SII and CRP, only SII remained a significant independent predictor, whereas CRP became less relevant. [114] This study seems to demonstrate that an increased SII was a significant independent predictor of long-term MACCE and stroke incidence in patients who underwent CAS. [106] Furthermore, SII appeared superior to CRP as an inflammatory indicator of prognosis associated with cardiovascular and cerebrovascular diseases. [114]

In retrospective study of Scalise et al [89] the aim is analysis of inflammation biomarkers in CEA and CAS to determine their predictive value for post-procedural restenosis risk. The cohort comprised 100 patients, 68 undergoing CEA and 32 undergoing CAS. [89] This study found predictive models using preintervention inflammation indices to identify restenosis cases post-revascularization, but the models need external validation. [81] Neutrophils-to-lymphocyte ratio (NLR) and systemic immune inflammation response index (SII) proved independent predictive biomarkers of restenosis at 12-month follow-up. [89]

CHAPTER 4: DUAL-LAYER MICROMESH STENT REAL-WORD EXPERIENCE: REVIEW AND META-ANALYSIS

4.1.1 INTRODUCTION

Endovascular treatment for carotid artery stenosis represents a minimally invasive approach that is living a new interest in vascular surgery field. In the latest 10 years a new technology based on dual-layer micromesh (DLMM) folding for carotid artery stent (CAS) has strongly influenced the choose for the best treatment. The so-called first generation of carotid stents, represented by open cells and closed cells stents, dominated for more than a decade the technology choose for CAS. At the same time, the growing CAS expertise, better patient selection, lesion-tailored strategies and evermore advanced techniques and devices continuously improve CAS outcomes. 2023 European guidelines recommend CAS in patients at high risk for surgery [115]. While CAS provides a minimally invasive alternative to CEA, the risk of peri- and early post-procedural distal embolization events with potential neurological sequelae warrants further attention.[116] DLMM stent were specifically designed for improved lesion coverage and prevention of plaque prolapse through the stent struts, to minimize the ischemic events during and after CAS. Different materials (nitinol or cobalt–chromium) and shapes (tapered vs. straight) of carotid artery stents provide a range of geometries and mechanical properties.[117] Characteristics such as high flexibility are needed to preserve vessel contours and radial force, wall apposition, and plaque coverage are required to prevent late embolic release. Despite the variety of available carotid artery stents, there remains the desire to develop and improve the materials and designs in order to achieve sustained, permanent embolic protection. [118] DLMM stents are thought to minimize the embolic potential from the plaque,[1] and are represented by two products, Roadsaver /Casper (Terumo Corp., Tokyo, Japan) and C-Guard (InspireMD Inc., Boston, Maryland, USA), both of which showed encouraging preliminary results. In this chapter we present a review of Literature about use of Roadsaver stent for treatment of carotid artery stenosis and a meta-analysis to evaluate the 30-day stroke rate, 30-day death rate and restenosis rate in comparison with first generation carotid stents. In addition, we perform meta-analysis to understand if there is some differences about ISR results between two DLMM stent, as recently suggested in Literature [119].

4.1.2 ROADSAYER STENT TECHNOLOGY DETAILS

The Roadsaver stent is constructed of an inner nitinol micromesh woven onto an external closed-cell stent to achieve a cell size of ~375 to 500 μm (Figure 1), one quarter that of the smallest cell size currently available. This structure is in grade to act as a trap for embolic material against arterial wall. The device is retrievable and repositionable (recommended with up to 50% deployment). Because of the braided mesh double layer design, the stent tapers according to the mismatching between internal and common carotid artery diameter. The low profile enhances cross-ability for primary stenting also in complex aortic arch anatomies.

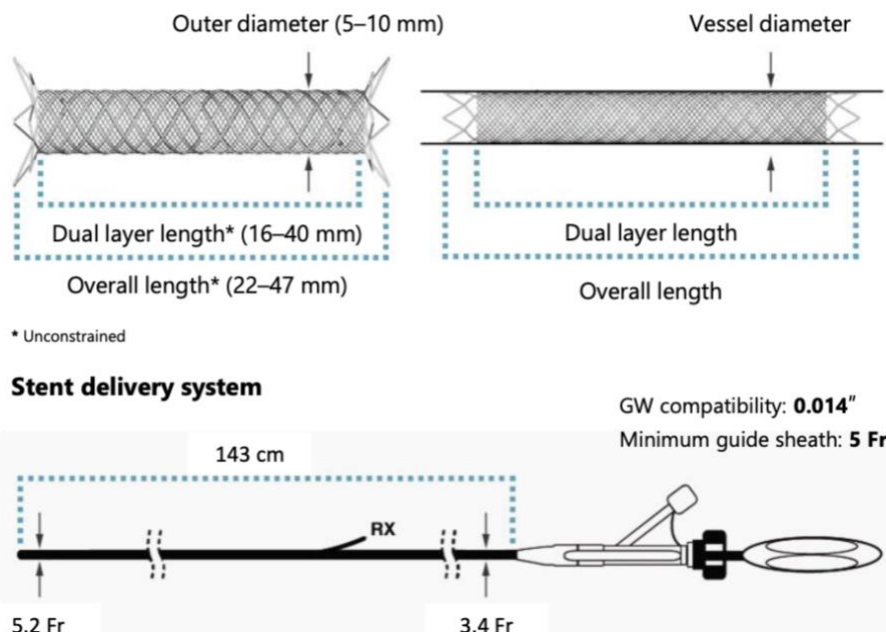


FIGURE 4 ROADSAYER STENT CHARACTERISTICS

4.2.1 MATERIAL AND METHODS

The systematic review and meta-analysis were performed according to the Cochrane Collaboration recommendations [120]. A rigorous protocol was established before the analyses, concerning all the objectives, inclusion and exclusion criteria, primary and secondary outcomes, and synthesis methods. We reported the results according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [121] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [122] recommendations.

4.2.2 LITERATURE SEARCH STRATEGY

Electronic databases, including PubMed, Embase and Cochrane were searched in the period interval between January the 1st 2014 and December 31st 2025, for potentially eligible European studies published in English language. The reference lists of the gathered reports were manually searched for relevant articles. The following medical keywords were used: “Roadsaver”, “Dual-layer micromesh”, “Roadsaver carotid stent”. We did not use the “Casper” term (the other name of Roadsaver stent for Asia).

4.2.3 CLINICAL OUTCOMES OF INTEREST

Typically reported 30-day clinical endpoints were death (D) and any stroke (S). In this study we identified as 12-month endpoint the in-stent restenosis (ISR). Those endpoints were further used for data comparisons.

4.2.4 STUDY ELIGIBILITY AND QUALITY ASSESSMENT

Studies eligible for screening needed to satisfy the criteria of at least 30 subjects, de novo atherosclerosis, extracranial carotid procedure and European population. Both prospective and retrospective studies were considered. A total of 17 records were initially identified. Besides the initial screening criteria, the following requirements were applied: (1) publication in English, (2) original study publication, (3) human subjects, (4) stenosis $\leq 99\%$. Quality assessment was performed to identify bias in at least one of five bias categories (patient selection/recruitment, performance in relation to study device(s), performance other than in relation to study device(s), outcome detection, and attrition and reporting; these led to 5 records (tab. II).

4.2.5 SELECTION CRITERIA

Two investigators independently performed a literature search. The two investigators independently reviewed the titles and abstracts of all citations to identify potentially relevant studies and to exclude duplicates. The investigators reviewed the full text of the corresponding publications to assess if the studies met the inclusion criteria. The references from the articles obtained were also analyzed. The literature search focused solely on articles published in peer-reviewed journals, to enhance the methodological rigor of studies examined. Only trans-femoral CAS procedures were considered: data in the same series of tandem lesions of the proximal common carotid artery or the intracranial arteries (e.g. thrombus removal) were excluded and not considered for the meta-analysis. Studies including treatment for complete carotid occlusion were not included. Studies were excluded from quantitative pooled analysis if (1) they included only tandem lesions; (2) they overlapped with other papers by the same institution (in such cases, the paper chosen for the meta-analysis was the most recent one, or the one with more useful details); (3) dual antiplatelet therapy was not administered after carotid stenting (no specific analysis about the type of antiplatelet was performed). If the data allowed to exclude the cases with tandem lesions or acute occlusion, the paper was considered for the meta-analysis; otherwise, the study was omitted from meta-analysis. The final inclusion of the studies was based on agreement between the reviewers. Any disagreement was resolved by discussion and consultation with the other coauthors.

4.2.6 DATA EXTRACTION

Data were extracted by two investigators working together using a predefined data extraction form. In case of disagreement, a third investigator reviewed the publication pertaining to a given study and a consensus was reached.

4.2.7 DATA SYNTHESIS

The baseline demographics and outcomes were extracted. In the case of more than one publication referring to 30-day or 12-month outcomes from a particular study, the data were integrated.

4.2.8 STATISTICAL ANALYSIS

Outcomes of interest are presented as frequency and percentage (%) as well as risk ratios (95%CI) for between-group comparisons. The pooled risk was estimated from individual studies by using random effects models calculating the Log Peto's odds ratio (OR) with relative 95% confidence interval. We used the heterogeneity χ^2 (Cochran Q) statistic to formally analyze heterogeneity across included studies. When Cochran Q p-values was < 0.10 , we pooled risk estimates using random effects models. The heterogeneity was also represented by I² index. The potential for publication bias was assessed using a

funnel plot in conjunction with weighted Weighted Egger. The analysis was carried out with Stata v20.0 (Stata Corp., TX, USA).

4.3 RESULTS

We found 22 European studies published on principal on-line libraries (PUBMED, EMBASE,...) in the years 2014-2024 about use of Roadsaver stents (tab II). Studies published are: 1 randomized controlled trial (RCT), 18 observational study, 3 case-series. We observed results from 3539 patients treated with dual-layer micromesh Roadsaver stent in more than 20 countries. 39% of these patients had a symptomatic carotid stenosis. We registered from Literature examined a total of 56 30-day stroke events (30-day stroke rate 1.58%) and 19 30-day death event (0.5%). Comprehensive-ISR rate is not calculated because not all studies report this outcome.

TABLE II RESULTS FROM REVIEW OF LITERATURE

Study	Year and type of study	Type of study	Population (symptomatic stenosis)	30-day outcomes
1) Hopf-Jenses et al. [118]	2015	Case Series (CS)	7 (7)	Stroke 0 Death: 0
2) Kedev et al. [123]	2015	CS	10 (0)	Stroke 0 Death: 0
3) Castagno et al. [124]	2016	CS	4 (0)	Stroke 0 Death: 0
4) Bosiers et al. [125]	2016	Retrospective study (RS)	100 (31)	Stroke: 1 Death:1
5) Ruffino et al. [126]	2016	Prospective study (PS)	23 (14)	Stroke 0 Death: 0
6) Nerla et al. [127]	2016	Multicenter RS	150 (43)	Stroke 0 Death: 0

7) Machnik et al. [128]	2017	RS	40 (21)	Stroke 0 Death: 0
8) Umemoto et al. [129]	2017	PS	5 with Roadsaver (0)	Stroke 0 Death: 0
9) Bosiers et al. [130]	2018	Multicenter RS (CLEAR-ROAD)	100 (31)	//
10) Nerla et al. [131]	2018	Multicenter RS (Italian registry)	150 (43)	//
11) Ruffino et al. [132]	2019	PS	25 with Roadsaver (15)	stroke 0 death:0
12) Ierardi et al. [133]	2019	RS	13 (11)	stroke 0 death:0
13) Montorsi et al. [134]	2020	RCT	54(9)	Stroke:0 Death:1
14) Machnik et al. [135]	2020	RS	287 (89)	Stroke:5 Death:1
15) Kahlberg et al. [136]	2021	RS	97 (35)	Stroke: 0 Death:0
16) Langhoff et al. [137]	2025	Multicenter RS (ROADSAVER)	1965 (971)	Stroke:37 Death:15
17) Petkoska et al. [138]	2022	PS	105(84)	Stroke:1 Death:1
18) Lamarca et al. [139]	2023	RS (ENROAD)	85(64)	Stroke:0 Death:0

19) Squizzato et al.[140]	2024	RS	242 (0)	Stroke:4 Death:0
20) Silvestri et al. [141]	2024	Multicenter RS	353(21)	Stroke:7 Death:0
21) Stefanini et al. [142]	2024	RS	38 (not specified)	Stroke: 1 Death:0
22) Pasqui et al [136] ¹	2024	RS	57 (not specified)	Stroke and death not differentiated by stent

We removed for our meta-analysis the 3 case-series and performed a metanalysis for outcomes of study with DLMM Roadsaver and first generation stent (FGS) based on data from these studies:

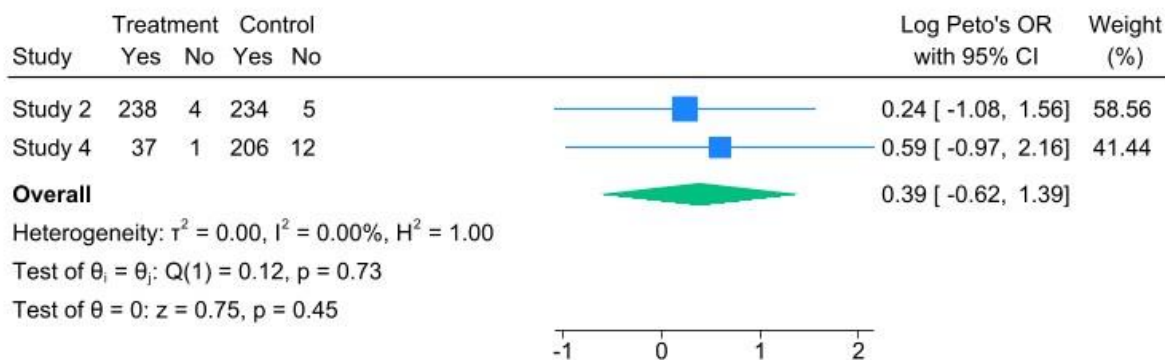
TABLE III STUDIES INCLUDED IN META-ANALYSIS

Studies	Year of publication	Nationality	Design	Comparison
1) Kahlberg et al [129]	2021	Italia	RS	Roadsaver Vs FGS
2) Squizzato et al [140]	2022	Italia	RS	Roadsaver Vs FGS Vs Cguard
3) Ruffino et al [132]	2019	Italia	PS	Roadsaver Vs C-Guard

¹ This study was not included in comprehensive 30-day stroke rate and comprehensive 30-day death rate because lack of data about these outcomes.

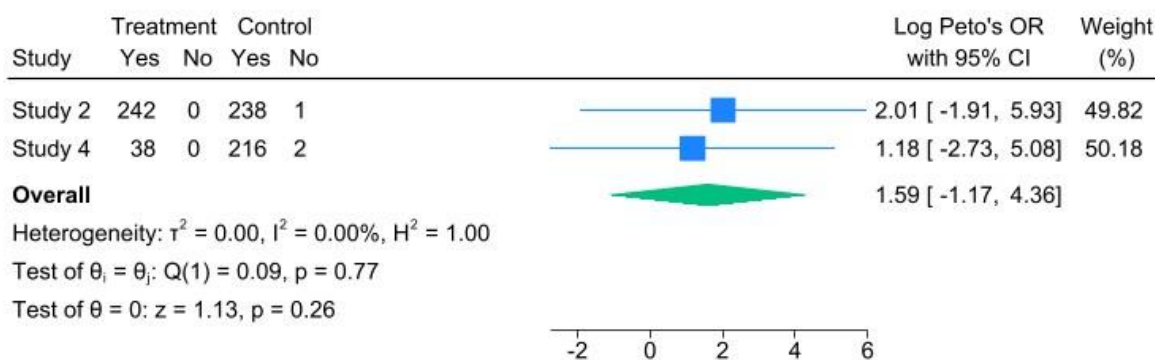
4) Stefanini et al. [142]	2024	Italia	RS	Roadsaver Vs FGS Vs C-guard
5) Pasqui et al. [143]	2024	Italia	RS	Roadsaver Vs FGS Vs C-guard

30-day strokes do not show any significant statistical differences with first generation of stent no heterogeneity was found, as reported below:



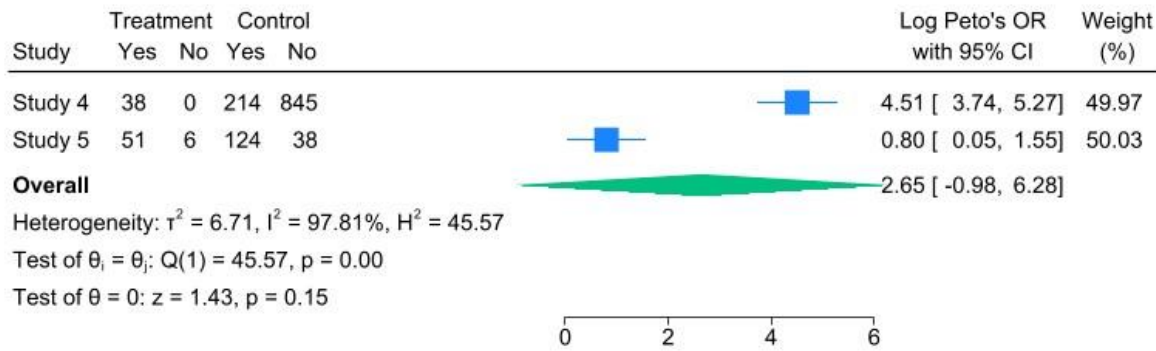
Random-effects DerSimonian-Laird model

30-day death rate do not statistically differ between DLMM Roadsaver stent and FS stent and no heterogeneity was found, as reported below:



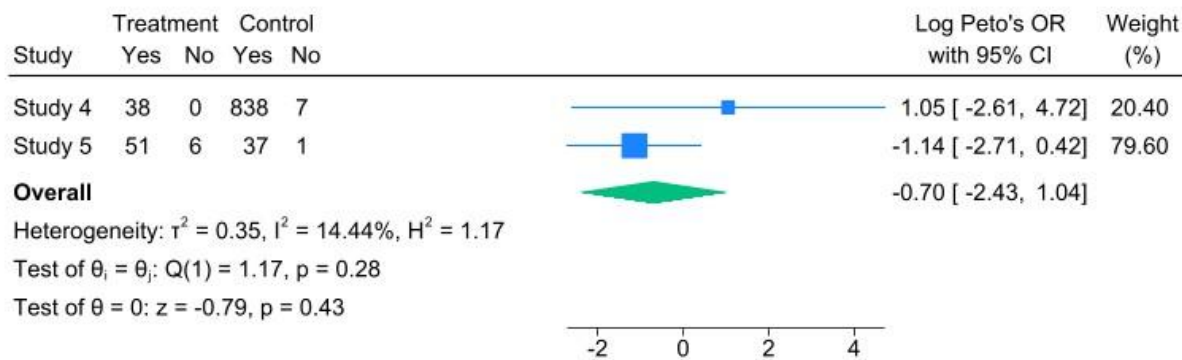
Random-effects DerSimonian-Laird model

Our analysis do not show any significant statistical difference between patients treated with DLMM Roadsaver and FS stent (with a high heterogeneity grade) in term of ISR, as reported below:



Random-effects DerSimonian–Laird model

As secondary outcome, we analysed if there was a statistical differences in term of ISR, between DLMM Roasaver and C-Guard stent. Our results do not show any significative statistical differences for restenosis rate between the two different existing DLMM devices with a low heterogeneity, as reported below:



Random-effects DerSimonian–Laird model

4.4 DISCUSSION

Results from this meta-analysis are represented by:

- No statistical differences in term of 30-day stroke in patients undergoing CAS between FGS and DLMM Roadsaver;
- No statistical differences in term of 30-day death in patients undergoing CAS between FGS and DLMM Roadsaver;
- No statistical differences in term restenosis-rate in patients undergoing CAS between FGS and DLMM Roadsaver;
- No statistical differences in term of restenosis-rate in patient undergoing CAS between DLMM Roadsaver and C-Guard.

The stent in carotid artery intervention plays a unique role in that after the embolic protection system has been removed, the stent is the main line of defense (along with antiplatelet therapy) against embolic and thromboembolic complications that may arise from the newly remodeled plaque with the varying degree of plaque coverage dependent on the stent design [144]. In this meta-analysis we analyzed studies with a similar design (observational studies, retrospective and perspective) and exclude

the only RCT study: the randomization and control group, even though hopeful, are absent in other studies. We found a high heterogeneity grade only in ISR analysis between FGS and DLMM Roadsaver group, while it was low for stroke-rate, death rate and for secondary outcome ISR rate between DLMM Roadsaver and C-Guard group. Several factors may contribute to high heterogeneity within the pool of CAS data available today. These include differences in study populations (proportion of symptomatic and asymptomatic patients) and different specialties performing the procedures (resulting in differences in patient selection for CAS). Most recent an upcoming studies show event rates consistent with the meta-analytic model. In 2023 Desantis et al.[145] published results of CATACLISMA (Carotid Artery sTenting And CeLI-area Impact on Stroke and Major Adverse events study), a multicenter, retrospective, financially unsupported physician-initiated observational cohort study conducted by 6 Italian tertiary referral hospitals conducted on asymptomatic carotid artery stenosis ranging from 70% to 99% undergoing transfemoral CAS. A total of 1096 CAS were considered (787 men, 71.8%, median age = 74 years). Three groups were defined based on the cell area: open cell design (OC, 547), closed cell design (CC, 344), dual-layer design (DL, 205) [145]. The employed DL stents were 159 Roadsaver and 42 C-Guard.[145] In Desantis et al. analysis, no statistical differences were observed in terms of 30-day stroke rates among groups (1.5%, OC: 1.1%, CC: 2.3%, DL: 1%, $p=0.27$), although more patients in the CC group suffered from a stroke event (2.3%, divided equally between major and minor stroke) compared with others, whereas only 2 (minor) stroke were accounted in the DL group.[145] In addition, no gender variable was also evaluated showing no differences between the 3 groups at multivariate analysis.[145] The good outcome in the asymptomatic patients of CAS in the real-world studies can be due to a lower vulnerability of the carotid plaque in these patients; furthermore, a quote of events are probably determined mainly by the aortic navigation and carotid catheterization that are a source of cerebral embolization independently from the carotid stent used.[146] On the other hand, the low rate of stroke in symptomatic patients (included in this meta-analysis), treated with DLMM can be justified by the design of the stents and the low risk of plaque prolapse or micro-embolization after stent apposition.[147] In Montorsi et al. RCT [134] we observed a comparison of the double-layer Roadsaver stent (RS) with the single-layer Carotid Wallstent (CW) (Boston Scientific, Santa Clara, California) in association with either distal embolic protection with the FilterWire (FW) device (Boston Scientific) or proximal protection with the Mo.Ma Ultra device (Medtronic, Santa Rosa, California) in patients with lipid-rich carotid plaques. A total of 104 consecutive patients with carotid artery stenosis were randomized to CAS with FW + RS (group 1, $n=27$), FW + CW (group 2, $n=25$), Mo.Ma + RS (group 3, $n=27$), or Mo.Ma + CW (group 4, $n=25$).[134] Study included all de novo carotid artery stenosis either symptomatic (Doppler peak systolic velocity [PSV] ≥ 130 cm/s and $>50\%$ stenosis) or asymptomatic (Doppler PSV ≥ 230 cm/s and $>70\%$ stenosis).[134] The primary endpoint was the number of micro embolic signals (MES) on transcranial Doppler among groups in the following CAS steps: 1 and 2) target vessel access; 3) lesion wiring; 4) pre-dilation; 5) stent crossing; 6) stent deployment; 7) stent dilation; and 8) device retrieval and deflation.[134] In this RCT[134] the RS was associated with a significantly lower MES count compared with the CW. Interestingly, spontaneous MES occurred in 29% of patients.[134] This finding is likely due to plaque prolapse(PP)-induced debris embolization between the last CAS phases.[134] Although not statistically significant, the risk for spontaneous MES was increased by 80% in patents with the CW compared with the RS.[134] These results further support the role of PP as a potential source of ischemic events in the late phase of CAS, fueling the role for a double-mesh stent for optimal plaque containment and reduction of PP.[134] Nerla et al. [127] found PP rate (by optical coherence tomography) as low as 7.7% in a small subgroup of patients who underwent CAS with the RS. It is interesting to note that most patients had evidence of PP between the 2 stent meshes, as proof of the protective effect of double mesh.[127] The RS significantly decreased the rate of

MES compared with the CW, especially when combined with the Mo.Ma system. [127] Squizzato et al. [140] suggested that a DLMM stent design is overall associated with a lower rate of intra-operative embolization and a lower embolic filter debris load, compared with open cell stent and closed cell stent. This seems to be the consequence of a lower embolic filter debris load in the micromesh stent group in the case of hypoechogenic plaques ($P < 0.001$), plaque length > 15 mm ($P = 0.015$), and presence of preoperative ipsilateral cerebral ischemic lesions ($P < 0.001$). [140] A possible explanation is that these plaque characteristics identify a subgroup of carotid stenotic lesions that are more prone to embolization during stenting procedures. [140] Hypoechogenic carotid lesions are typically associated to the presence of a soft component, and previous studies [148][149] had described the association between echolucency and the amount of embolic material captured by the filter. In addition, the presence of preoperative ischemic cerebral lesions may be considered a sign of silent embolization from an unstable asymptomatic carotid stenosis [150][151] that poses a greater risk of embolization also in the perioperative period [148][152]. Differently, the length of the lesion is not associated to the quality of the atheroma, but is directly linked to the surface of the carotid plaque; therefore longer plaques carry an higher embolic risk due to the wider area of embolic source. [140] This new-generation micromesh carotid stents has a peculiar configuration derived from the idea that a smaller cell area would protect from perioperative adverse events, [116] and in fact the resulting cell area ($75\text{--}500\text{ }\mu\text{m}$ for the Roadsaver stent [13] is significantly smaller compared with traditional OCS (5.89 mm^2 for the Precise) and CCS (1.08 mm^2 for the Wallstent) stents. [118] This design is specifically intended to provide an optimal plaque scaffolding and prevent plaque prolapse through the struts of the stent, that has been associated with both intraoperative and perioperative embolization in patients undergoing CAS [140]. Squizzato et al. [140] found the use of micromesh stent (Roadsaver for this study) seems to be associated with a lower embolization rate and embolic filter debris load, especially in hypoechogenic and long plaques and in patients with pre-operative evidence of asymptomatic ischemic cerebral lesion. It is important clarify that the occurrence of new magnetic resonance imaging lesions, as well as the embolic filter debris load, represents a surrogate end point of Squizzato et al. study and only a minority of patients with new magnetic resonance imaging lesion or filter embolization develop clinically evident neurological complications. [140] On the other hand, the same group of University of Padua reported [140] significant relationship existing between the amount of embolic filter debris and the risk of clinically evident neurological complications. Despite the significant difference in embolic filter debris load, the clinical outcomes in terms of neurological complications were similar between the 3 aforementioned group of stents and further studies are required to clarify the impact of stent design on intraoperative or postoperative stroke. [140] Moreover, in Roadsaver study, Langhoff et al. [137] found specific types of high-risk anatomies did not significantly influence the observed outcomes: higher numbers of anatomical complexities did not seem to associate with an elevated risk of either 30-day MAEs or any stroke. [137] These findings suggested that micromesh carotid stent (Roadsaver in this study) use in CAS may mitigate the risks associated with complex vascular anatomies. [137]. Mazurek et al. [153] review and meta-analysis of the clinical data of 68,422 patients (112 studies) treated using first generation carotid stent or new generation carotid stent (C-Guard and Roadsaver) demonstrated that outcomes at 30 days (death/stroke/MI) were significantly improved for pooled “mesh stents” in relation to first generation stents. The benefit was present for new generation stents against both open and closed-cell first generation carotid stent. [153] Mazurek et al. suggested that the two new generation carotid stent types significantly differ (both in their outcomes related to first generation stent and for outcomes within the new generation carotid stent group) indicating lack of any carotid ‘mesh-stent’ class effect, but this found was not evident in other contemporary meta-analysis. [153] In fact, In Pini et al. [154] CAS with micromesh carotid stent is associated to a low rate of 30-day stroke in both symptomatic (1.9%) and asymptomatic

(1.5%) patients and the type of micromesh stent (C-Guard or Roadsaver) did not affect the 30-day stroke rate.[154] In addition, in this meta-analysis, acute micromesh carotid stent occlusion was separately evaluated. [154] Some authors considered the acute micromesh stent occlusion as a specific complication of the design of these stents. [154] The rate of DLS occlusion reported in Pini et al. meta-analysis is 0.8% over a total of 930 patients.[154] These results are strikingly different from the data of Runck et al. [155] and Yilmaz et al. [156] who reported a 24% and a 45% micromesh stent thrombosis rate in the treatment of acute strokes, respectively (including tandem lesions). The micromesh thrombosis rate reported by Pini et al.[154] seems to be similar to the results reported by Moulakakis et al. [157](who described a series of 674 CAS with standard stents, having four cases (0.6%) of acute thrombosis, possibly secondary to carotid dissections and overlapping of a second stent).[154]

Our results seem in line with Pini et al.[154] results, with a low 30-day stroke rate and low 30-day death rate even though no statistical differences merged in comparison with first generation carotid stent. In addition, no statistical differences merged from meta-analysis between in-stent restenosis rate between two different type of new generation carotid stents.

The present meta-analysis has some limitations, firstly the retrospective nature of all studies and the absence of a standardized neurological evaluation, leading to a possible underestimation of stroke rates. The experience and the volume of the centers have a determinant role in the CAS outcome, with a reduction of neurologic events in high experience centers; however, it was not possible to investigate this moderator in our meta-analysis.[158] On the other hand, in recent Roadsaver study [152] merged, although there may be slight differences in patient selection and procedural preferences across different specialties, outcomes achieved in real-world practice remain similar when performing contemporary CAS procedures using modern devices and techniques. [159]

4.5 CONCLUSIONS

This meta-analysis of DLS for CAS suggests that the 30-day stroke rate with micromesh carotid stent Roadsaver is low and no statistical differences merged in comparison with first generation carotid stent for 30-day death rate and in-stent restenosis rate. As a secondary outcome, no statistical differences in term of in-stent restenosis rate merged between two different type of new generation micromesh carotid stent. 2023 European Society for Vascular Surgery guidelines suggests, in the new Recommendation 84, for patients undergoing elective carotid artery stenting, dual layer mesh covered stents may be considered (Class IIb, Level C), but caution should be exercised if considering dual-layer mesh in acute stroke treatment. [160] However, further studies are necessary to confirm the findings of these retrospective series with prospective data. Hopefully, this work provides several clinically relevant hypotheses for further testing in large randomized and controlled trials powered for clinical endpoints.

CHAPTER 5: THE DI.GE.STENT.IIS STUDY

5.1 INTRODUCTION

Large randomized clinical trials were not designed to analyze and distribute events by gender. Most of the information regarding women was derived from either post hoc analyses or studies, which underrepresented women. Regarding carotid stenting procedure, the impact of gender on procedural outcomes has not yet been well defined. The existing literature has suggested several risk factors, such as vessel diameter, plaque composition, sensitivity to antiplatelet therapy, hormones, as potential mechanisms for gender differences in outcomes after CEA. It has also been shown that atherosclerotic plaque is relatively stable in women, female carotid arteries are high-velocity vessels with an increased inflow/outflow ratio, and they tend to have relatively localized lesions compared to men. These factors are generally associated with favorable short-term and long-term outcomes after carotid endovascular treatment. On the other hand, women tend to have atherosclerotic plaque distributed primarily in the common carotid artery compared to the proximal internal carotid artery, which is usually seen in men. This represents a risk during CAS, especially in symptomatic patients with unstable and friable plaques. The discrepancy in results between different studies continues to fuel the debate about the possible influence of gender on peri- and post-operative outcomes in CAS. In addition, the possible predictive role of some biomarkers used in oncology field (as reviewed in chapter 3) is a “hot topic” in vascular surgery, as highlighted in the 2021 study by Keskin et al. [82] and other authors [89] in following years. This biomarker is candidate for use as a simple and practical indicator to identify high-risk patients undergoing CAS. We indagated the role of gender, the role of new technology and the role of inflammation in CAS through SII and NLR biomarkers in this study.

5.2 MATERIAL AND METHODS

5.2.1 STUDY DESIGN

This is a retrospective and prospective, observational, cohort study conducted in a three Italian tertiary centers of vascular surgery, started in November 2022. From January 2015 to December 2025, we observed patients with carotid artery stenosis underwent transfemoral CAS. (see fig.1 and 2) In our series we grouped our patients for gender, stent technology and SII value. For each group we analyzed demographics and comorbidities as preoperative data (table I). Comorbidities were defined based on the indications of the Society for Vascular Surgery reporting standards. Intraoperative details included: supra-aortic-vessels (SAV) CT-angiography study, target carotid stenosis, contralateral carotid stenosis, symptomatic stenosis, symptoms, contralateral carotid intervention, contralateral carotid stenting, site, type of anesthesia, general anesthesia conversion, type of intervention, embolic protection device (EPD), type of EBD, stent diameter (mm), stent length (mm). Post-operative data included access-site and systemic complications and type of anti-platelet medication drugs used.

TABLE I

Demographics and comorbidities data
Age (years)
Chronic Ischemic Cardiomyopathy
Peripheral Artery Disease (PAD)
Hypertension
Diabetes
Smoking habit
Aortic aneurysm
Contralateral ICA occlusion

Dual antiplatelet therapy is initiated postoperatively (unless otherwise indicated in the specific case) for a minimum of 1 month. Data will be collected on the immediate postoperative results (return to the ward and subsequent 24 hours of hospital observation (or possibly more hours of hospital stay depending on the specific case).

An initial follow-up examination is scheduled within the first 3 months, preferably:

- 1 month after the procedure and a subsequent examination is scheduled within 6 months from procedure;
- 12 months after the procedure and then annually thereafter (unless otherwise indicated based on the clinical picture)

FIG.1 PERSPECTIVE PART OF THE STUDY (JANUARY 1ST 2023 – DECEMBER 31TH 2024)

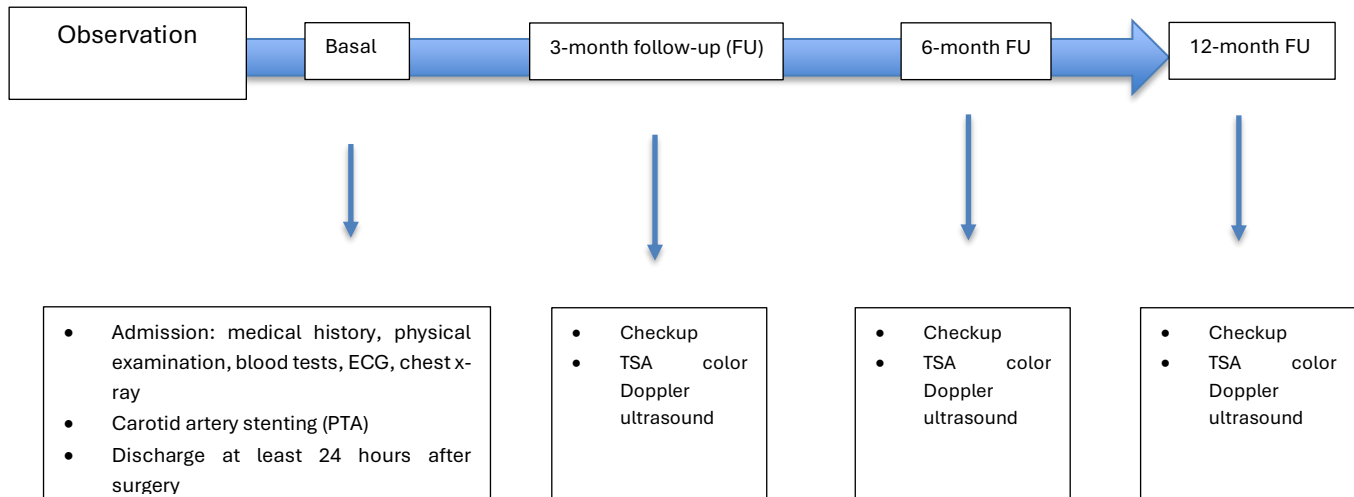
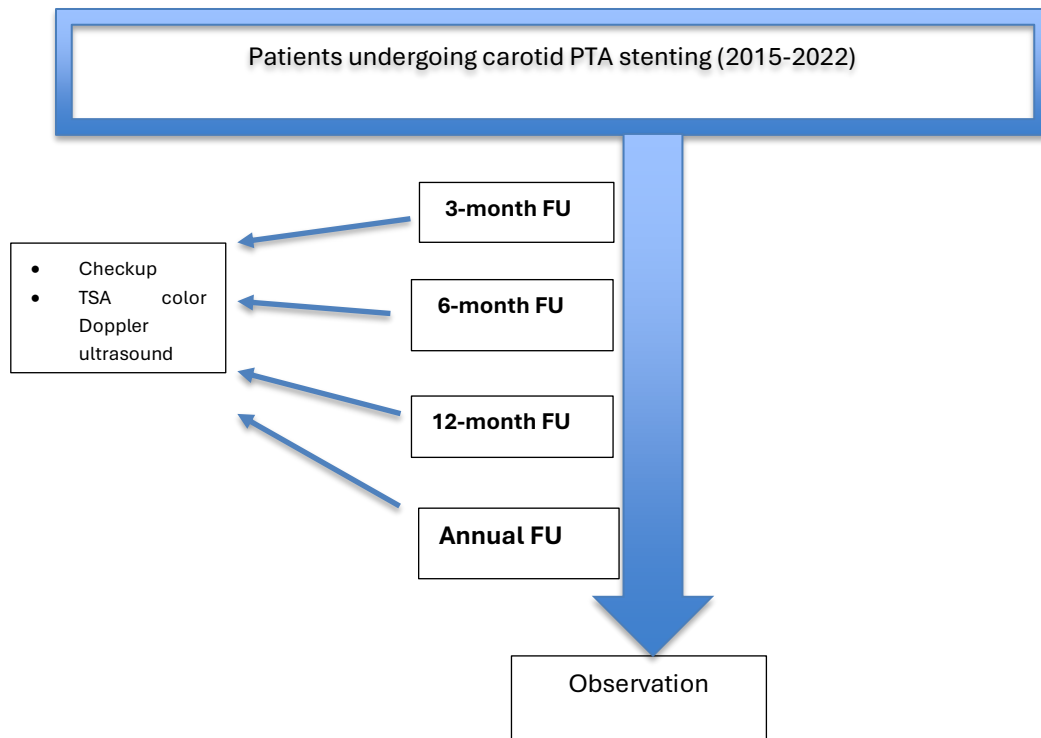


FIG.2 RETROSPECTIVE PART OF THE STUDY



5.2.2 PATIENT'S CONSENT

For perspective part of the study, upon admission to the Vascular Surgery Unit for carotid PTA stenting surgery, the patient will be given a document outlining their informed consent for the procedure, along with a simultaneous interview with the surgical and anesthesiology team. After obtaining informed consent, the patient's medical history is recorded.

5.2.3 ETHICAL COMMITTEE APPROVAL

The study will be conducted in accordance with the Independent Ethics Committee (IEC), the ICH GCP Guidelines, in accordance with the regulations regarding clinical safety data management (E2A, E2B(R3)), with the European Community directives 2001/20, 2001/83, 2003/94 and 2005/28, as amended by local law and with the ICH Guidelines relating to scientific integrity (E4, E8, E9, E10). Furthermore, it will comply with all local regulatory requirements and those for data protection in force at the IRCCS Fondazione Casa Sollievo della Sofferenza of San Giovanni Rotondo (FG). This study has been approved May 17th 2023 by Hospital Ethical Committee in IRCCS Fondazione Casa Sollievo della Sofferenza with code Di.Ge.STENT.IIS (Italian as official language, titled "Differenze di genere nei risultati immediati e a distanza con l'utilizzo degli stent di ultima generazione nel distretto carotideo e ruolo dell'indice di immunoinfiammazione sistemica come biomarker di rischio per i risultati immediati e a distanza").

5.4 OBJECTIVES

The primary outcome of the study are the immediate, medium, and long-term:

- ipsilateral stroke-free survival (primary outcome);
- all-cause death-free survival;
- MACE-free survival (TIA, stroke, AMI, and death);
- restenosis-free survival (secondary outcome)

In patients undergone to a PTA stenting for carotid artery stenosis in three tertiary center for endovascular surgery between 2015 and 2024 considering the gender variable and stent technology used.

Furthermore, the study aims to measure, observe, and analyze the systemic immuno-inflammation index (calculated as the product of the platelet count and the neutrophil count, divided by the lymphocyte count), as a potential indicator of outcome risk in patients with carotid artery stenosis undergoing carotid artery stenting (PTA).

5.4.1 PRIMARY OBJECTIVES

1. Ipsilateral stroke-free survival. Observation of ipsilateral stroke (defined as a neurological event lasting more than 24 hours with signs and symptoms consistent with the cerebral hemisphere to which the internal carotid artery being studied belongs) will determine the achievement of the clinical endpoint.
2. Death-free survival (all causes).
3. MACCE (Major Adverse Cerebro-Cardiovascular Event)-free survival: clinical observation at follow-up of TIA (a neurological event consistent with the side of the treated carotid stenosis lasting less than 24 hours), stroke, myocardial infarction (according to the 4th universal definition) and death.

5.4.2. SECONDARY OBJECTIVES

1. Restenosis-free survival. Restenosis represents the recurrence of a reduction in caliber (greater than 50%) of the internal carotid artery that has undergone surgery. This will be searched for from the color Doppler ultrasound examinations of the epiaortic vessels that patients undergo during follow-up.
2. Systemic immune-inflammation index (surrogate endpoint): the measurement of IIS preoperatively is obtained from the blood tests that all patients who are candidates for PTA carotid stenting undergo upon admission. A correlation will be sought between the value of the biomarker thus obtained and the aforementioned endpoints.

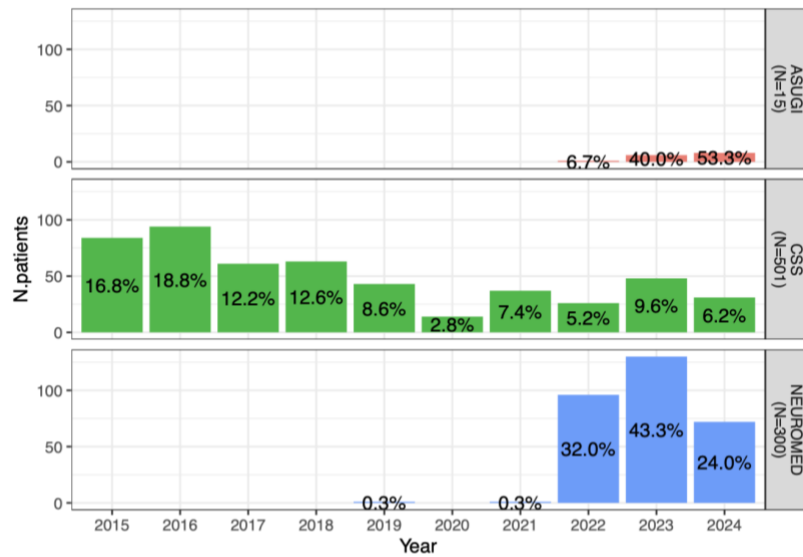
5.5. STATISTICAL ANALYSIS

For continuous variables, patient characteristics were summarized using the mean and standard deviation (SD), the median and interquartile range (IQR; first and third quartiles) and the minimum and maximum values. Between-group comparisons were performed using parametric or non-parametric tests, as appropriate. For continuous variables, the two-sample t test or ANOVA was used for comparisons between two or more groups, respectively, when data were symmetric and normally distributed (assessed by the skewness index and Shapiro-Wilk test); otherwise, the Mann–Whitney U or Kruskal-Wallis test was applied. Categorical variables were reported as absolute and relative frequencies (%) and were compared using the Chi-square or Fisher's exact test, as appropriate. Bar plots were generated to illustrate the distribution of transfemoral CAS procedures per calendar year across centers. Time-to-event analyses were conducted separately for each primary and secondary outcome. Follow-up time was defined as the interval between the admission and the occurrence of the event of interest or the last available follow-up (or last contact), whichever came first. A recursive partitioning survival tree was applied using the systemic immune-inflammation index (SII) as the sole splitting variable to identify patient subgroups with different restenosis-free survival profiles. The optimal SII thresholds derived from the final tree were used to classify patients into low- and high-risk groups for restenosis. Kaplan-Meier curves were constructed to estimate disease-free survival across strata defined by relevant prognostic factors, including SII categories derived from the survival tree, sex, dyslipidemia, stent type and clinically defined NLR categories. Differences between survival curves were assessed using the log-rank test. Univariable and multivariable Cox proportional hazards models were fitted to estimate hazard ratios (HRs) and corresponding 95% confidence intervals for each outcome. In the fully adjusted multivariable model, HRs were adjusted for age at hospitalization, smoking status, diabetes, stent type (first-generation vs double-layer), and dyslipidemia. To evaluate whether inclusion of the SII improved the discriminatory performance of the multivariable Cox model for predicting restenosis, time-dependent c-statistics were estimated before and after SII inclusion using Uno's method with 1,000 perturbation resampling at 1, 3, and 6-year follow-up. The difference between the c-statistics estimated by any two nested models were assessed using a z test. All statistical analyses and plots were performed using R software. A two-sided p value <0.05 was considered statistically significant.

5.6 RESULTS

5.6.1 POPULATION CHARACTERISTICS

We enrolled a total of 816 patients from IRCCS Fondazione Casa Sollievo della Sofferenza (San Giovanni Rotondo, FG), IRCCS Istituto Neurologico Mediterraneo (NEUROMED, Pozzilli, IS) and Azienda Sanitaria Universitaria Giuliano Isontina (ASUGI, Trieste) treated with PTA stenting for asymptomatic carotid artery stenosis between 70-99% (evaluated with carotid Doppler ultrasound and/or Computed Tomography Angiography of supra-aortic trunks)) and >50% for symptomatic carotid artery stenosis (according Italian SICVE guidelines [161]) (Fig.3).



These percentages refer to the total number of patients within each center

FIGURE 3 NUMBER OF TRANSFERMORAL CAS PROCEDURES PERFORMED PER CALENDAR YEAR AT EACH CENTER

In our population, we had 261 female (32%) and 555 male patients (68%). Mean admission age was 71.4 (+/-7.5) years old, middle admission age was 74.8 (69.4-79.5) years old; age range was wide (43.5 - 92.0 years old). (tab.II) Symptomatic carotid stenosis were 66 (8.1%) and 750 (91.9%) patients had asymptomatic carotid stenosis. 51.2% of patients treated (416) had a computed tomography angiography of supra aortic vessels. Stenosis treated were: less than 60% in 35 patients (4.3%), 533 (65.8%) with a stenosis between 60% and 80%, 242 patients (29.9%) between 80% and 99%. In 38 patients (4.9%) there was a contralateral occlusion of carotid artery. About symptomatic carotid stenosis, 17 patients suffered a TIA (2.1%), 12 patients had a minor stroke (1.5%) and 5 patients a major stroke (0.6%). Primary carotid artery stenting were 94.5%. Embolic protection devices were used in all case except 3(0.4%): distal filter in 99.1% (Angioguard device in 30.8%, Emboshield filter in 29.9%, not specified in 39.3%).

Stent used were:

- Precise PRO RX (Cordis, Miami, FL, USA) 108 (14.9%);
- Carotid Wallstent 230 (31.7%);
- Xact (Boston Scientific Corp,Natick, MA, USA) 143(19.7%);
- C-GUARD (InspireMD, Boston,MA, USA) 54 (7.4%);
- Roadsaver (Terumo, Tokyo, Japan) 190 (26.25%);

Local anesthesia used in all patients except one; in 2 patients needed shifting from local to general anesthesia (tab.II)

TABLE II PATIENT'S CHARACTERISTICS (SD: STANDARD DEVIATION; IQR: INTERQUARTILE RANGE (I.E. FIRST, THIRD QUANTILES) - 1. T-TESTFOR INDIPENDENT SAMPLES; 2. U DI MANN-WHITNEY TEST; 3. CHI-SQUARE TEST; 4. FISHER'S EXACT TEST

Patient's data	First generation (FS) (N=522)	Double layer (DL) (N=294)	Total (N=816)	p.value
Age				0.062
Mean (SD)	74.5 (7.2)	73.5 (8.1)	74.1 (7.5)	
Median (IQR)	75.1 (70.1, 79.5)	73.9 (68.3, 79.0)	74.8 (69.4, 79.5)	
Min - Max	47.7 - 92.0	43.5 - 89.8	43.5 - 92.0	
Hospital stay				<0.001
Mean (SD)	2.5 (16.9)	3.0 (21.8)	2.7 (18.8)	
Median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	
Min - Max	0.0 - 367.0	0.0 - 367.0	0.0 - 367.0	
Gender				0.995
Female	167(32.0%)	94 (32.0%)	261 (32.0%)	
Male	355 (68.0%)	200 (68.0%)	555 (68.0%)	
Aneurysm associated				0.575
N.missing data	7	5	12	
No	501 (97.3%)	283 (97.9%)	784 (97.5%)	
Si	14 (2.7%)	6 (2.1%)	20 (2.5%)	
PAD				0.069
	13	11	24	

N.missing data				
No	448 (88.0%)	236 (83.4%)	684 (86.4%)	
Si	61 (12.0%)	47 (16.6%)	108 (13.6%)	
Dyslipidemia				<0.001
N.missing data	4	3	7	
No	242 (46.7%)	59 (20.3%)	301 (37.2%)	
Si	276 (53.3%)	232 (79.7%)	508 (62.8%)	
Hypertension				0.001
N.missing data	6	2	8	
No	99 (19.2%)	26 (8.9%)	125 (15.5%)	
Si	417 (80.8%)	266 (91.1%)	683 (84.5%)	
Diabetes				0.137
N.missing data	11	7	18	
No	285 (55.8%)	178 (62.0%)	463 (58.0%)	
Tipo 1	1 (0.2%)	0 (0.0%)	1 (0.1%)	
Tipo 2	225 (44.0%)	109 (38.0%)	334 (41.9%)	
Smoking				0.076

N.missing data	8	5	13	
No	266 (51.8%)	127 (43.9%)	393 (48.9%)	
Si	81 (15.8%)	59 (20.4%)	140 (17.4%)	
Ex	167 (32.5%)	103 (35.6%)	270 (33.6%)	
Familiarity for PAD				0.248
N.missing data	4	5	9	
No	483 (93.2%)	263 (91.0%)	746 (92.4%)	
Si	35 (6.8%)	26 (9.0%)	61 (7.6%)	
Ischemic heart disease				0.947
N.missing data	26	5	31	
No	349 (70.4%)	204 (70.6%)	553 (70.4%)	
Si	147 (29.6%)	85 (29.4%)	232 (29.6%)	
Neutrophils (1000/mcl)				0.822 ²
Mean (SD)	5.5 (7.0)	4.7 (1.7)	5.2 (5.7)	
Median (IQR)	4.5 (3.6, 5.6)	4.4 (3.5, 5.5)	4.5 (3.5, 5.5)	
Min - Max	0.0 - 87.2	1.2 - 10.9	0.0 - 87.2	

Lymphocytes (1000/mcl)				0.169 ²
Mean (SD)	2.3 (4.6)	2.0 (1.6)	2.2 (3.8)	
Median (IQR)	1.7 (1.4, 2.1)	1.8 (1.3, 2.3)	1.7 (1.3, 2.2)	
Min - Max	0.2 - 80.0	0.4 - 25.5	0.2 - 80.0	
Platelets				0.945 ¹
Mean (SD)	219.7 (65.1)	220.0 (66.6)	219.8 (65.6)	
Median (IQR)	213.5 (174.2, 257.0)	211.0 (177.2, 254.8)	212.0 (176.0, 256.2)	
Min - Max	43.0 - 606.0	41.0 - 601.0	41.0 - 606.0	
Systemic immuno- inflammation index (SII)				0.245 ²
N.missing data	1	0	1	
Mean (SD)	720.4 (1051.6)	638.7 (482.1)	690.9 (889.7)	

Median (IQR)	538.9 (390.2, 789.3)	499.3 (367.0, 733.7)	525.4 (382.0, 775.0)	
Min - Max	24.0 - 15145.8	40.5 - 5449.1	24.0 - 15145.8	
SII tertiles				0.458 ²
N.missing data	1	0	1	
< 430.1	165 (31.7%)	105 (35.7%)	270 (33.1%)	
430.1 - 657.4	176 (33.8%)	97 (33.0%)	273 (33.5%)	
> 657.4	180 (34.5%)	92 (31.3%)	272 (33.4%)	
Neutrophil-to-lymphocyte ratio (NLR)				0.290 ²

N.missing data	1	0	1	
Mean (SD)	3.2 (3.8)	2.8 (1.5)	3.0 (3.2)	
Median (IQR)	2.5 (2.0, 3.4)	2.5 (1.9, 3.4)	2.5 (2.0, 3.4)	
Min - Max	0.1 - 64.7	0.1 - 9.7	0.1 - 64.7	
NLR (categoric cliniche)				0.904 ³
N.missing data	1	0	1	
< 1	10 (1.9%)	6 (2.0%)	16 (2.0%)	
1 - 3	329 (63.1%)	181 (61.6%)	510 (62.6%)	
> 3	182 (34.9%)	107 (36.4%)	289 (35.5%)	

TABLE IV INTERVENTION DETAILS - 3. CHI-SQUARE TEST; 4. FISHER'S EXACT TEST

Intra-operative and post-operative details	FS (N=522)	DL (N=294)	Total (N=816)	p.value
Pre-operative SAV CT-angiography study				<0.001 ³
N. missing data	3	1	4	
No	332 (64.0%)	84 (28.7%)	416 (51.2%)	
Yes	187 (36.0%)	209 (71.3%)	396 (48.8%)	
Target carotid stenosis				< 0.001 ³

N.missing data	4	2	6	
<60%	29 (5.6%)	6 (2.1%)	35 (4.3%)	
Between 60%-80%	381 (73.6%)	152 (52.1%)	533 (65.8%)	
Between 80-99%	108 (20.8%)	134 (45.9%)	242 (29.9%)	
Contralateral carotid stenosis				0.558 ³
N.missing data	15	26	41	
<60%	429 (84.6%)	225 (84.0%)	654 (84.4%)	
Between 60% and 80%	39 (7.7%)	26 (9.7%)	65 (8.4%)	
Between 80% and 99%	14 (2.8%)	4 (1.5%)	18 (2.3%)	
Occlusion	25 (4.9%)	13 (4.9%)	38 (4.9%)	
Symptomatic stenosis				0.163 ³
No	485 (92.9%)	265 (90.1%)	750 (91.9%)	
Yes	37 (7.1%)	29 (9.9%)	66 (8.1%)	
Symptoms				0.577 ⁴
N.missing data	4	2	6	
No	494 (95.4%)	282 (96.6%)	776 (95.8%)	
TIA	11 (2.1%)	6 (2.1%)	17 (2.1%)	
Stroke minor	10 (1.9%)	2 (0.7%)	12 (1.5%)	

Stroke major	3 (0.6%)	2 (0.7%)	5 (0.6%)	
Contralateral carotid intervention				0.985 ³
No	453 (86.8%)	255 (86.7%)	708 (86.8%)	
Yes	69 (13.2%)	39 (13.3%)	108 (13.2%)	
Contralateral carotid stenting				0.872 ³
No	492 (94.3%)	276 (93.9%)	768 (94.1%)	
Yes	30 (5.7%)	18 (6.1%)	48 (5.9%)	
Site				0.013 ³
Left carotid	242 (46.4%)	163 (55.4%)	405 (49.6%)	
Right carotid	280 (53.6%)	131 (44.6%)	411 (50.4%)	
Type of anesthesia				1 ⁴
N.missing data	2	0	2	
General	1 (0.2%)	0 (0.0%)	1 (0.1%)	
Local	519 (99.8%)	294 (100.0%)	813 (99.9%)	
General anesthesia conversion				1 ⁴
No	521 (99.8%)	293 (99.7%)	814 (99.8%)	
Yes	1 (0.2%)	1 (0.3%)	2 (0.2%)	
Type of intervention				0.003 ³
N.missing data	0	1	1	
Primary PTA stenting	484 (92.7%)	286 (97.6%)	770 (94.5%)	

Secondary PTA stenting	38 (7.3%)	7 (2.4%)	45 (5.5%)	
Embolic protection device (EPD)				0.065 ⁴
N.missing data	1	0	1	
None	3 (0.6%)	0 (0.0%)	3 (0.4%)	
Filter	517 (99.2%)	291 (99.0%)	808 (99.1%)	
Distal occlusive balloon	0 (0.0%)	3 (1.0%)	3 (0.4%)	
Reversal flow device	1 (0.2%)	0 (0.0%)	1 (0.1%)	
Stent device				<0.001 ³
N.missing data	41	50	91	
C-GUARD	0 (0.0%)	54 (22.1%)	54 (7.4%)	
PRECISE)	108 (22.5%)	0 (0.0%)	108 (14.9%)	
ROADSAVER	0 (0.0%)	190 (77.9%)	190 (26.2%)	
WALLSTENT	230 (47.8%)	0 (0.0%)	230 (31.7%)	
XACT	143 (29.7%)	0 (0.0%)	143 (19.7%)	
Stent categories				<0.001 ³
Open cell (OC)	112 (21.5%)	0 (0.0%)	112 (13.7%)	
Closed cell(CC)	410 (78.5%)	0 (0.0%)	410 (50.2%)	
Dual-layer micromesh (DLMM)	0 (0.0%)	294 (100.0%)	294 (36.0%)	
Type of EBD				<0.001 ³

Angioguard	237(45.4%)	14 (4.8%)	251(30.8%)	
Emboshield	158 (30.3%)	86(29.3%)	244 (29.9%)	
Not specified	127 (24.3%)	194 (66%)	321 (39.3%)	
Stent diameter (mm)				< 0.001 ⁴
7	186 (35.6%)	22 (7.5%)	208 (25.5%)	
8	163 (31.2%)	252 (85.7%)	415 (50.9%)	
9	168 (32.2%)	17 (5.8%)	185 (22.7%)	
10	5 (1.0%)	3 (1.0%)	8 (1.0%)	
Stent lenght (mm)				< 0.001 ³
20	0 (0.0%)	24 (8.2%)	24 (2.9%)	
25	1 (0.2%)	133 (45.2%)	134 (16.4%)	
30	231 (44.3%)	86 (29.3%)	317 (38.8%)	
40	290 (55.6%)	47 (16.0%)	337 (41.3%)	
50	0 (0.0%)	1 (0.3%)	1 (0.1%)	
60	0 (0.0%)	3 (1.0%)	3 (0.4%)	

5.6.2 IMMEDIATE RESULTS

Technical success was reached in 814 patients (100%, 2 missing data). About immediate post-operative complications, we registered: in 764 patients, no complication (94.1%), local complications (hematoma of the femoral access, pseudoaneurysm) in 18 people (2.2%) and systemic complications (arrhythmias, hypotension, hypertension, mental confusion) in 30 patients (3.7%). Post-operative therapy was: dual antiplatelet in 74.9%, Clopidogrel in 10% of patients, ASA in 5.5% (single antiplatelet therapy in 15.5% of patients), EBPM in 1.7%, other (Oral anticoagulant) in 7.9% of patients. 356 patients (95.4%) used statin therapy, not used in 17 (4.6%); ezetimibe used in 112 patient (30%). See tab.IV.

We separated our study population by stent type:

- First generation stents (FGS) composed by patients undergone to a PTA stenting with PRECISE PRO RX (22.7%); WALLSTENT (47.6%), Xact (29.7%);
- Dual-layer group (DL) composed by patients undergone to a PTA stenting with C-guard (22.5%) and Roadsaver (77.5%).

TABLE IV INTERVENTION PATIENTS DETAILS - 3. CHI-SQUARE TEST; 4. FISHER'S EXACT TEST

INTERVENTION DETAILS	FS (N=522)	DL (N=294)	Total (N=816)	p.value
Intra-operative control				
SAV+encephalic angiogram	522 (100.0%)	294 (100.0%)	816 (100.0%)	
Clinical signs				
N.missing data	2	0	2	
None	520 (100.0%)	294 (100.0%)	814 (100.0%)	
PO femoral access control				0.048 ³

No	14 (2.7%)	2 (0.7%)	16 (2.0%)	
Yes	508 (97.3%)	292 (99.3%)	800 (98.0%)	
Post-operative CT/MRI				<0.001 ³
N.missing data	2	0	2	
No	461 (88.7%)	285 (96.9%)	746 (91.6%)	
Yes	59 (11.3%)	9 (3.1%)	68 (8.4%)	
PO complications				0.522 ³
N.missing data	5	1	6	
None	483 (93.4%)	279 (95.2%)	762 (94.1%)	
Local	12 (2.3%)	6 (2.0%)	18 (2.2%)	
Systemic	22 (4.3%)	8 (2.7%)	30 (3.7%)	
PO Anti-platelet therapy				0.038 ⁴
N.missing data	117	170	287	

Cardioaspirin	24 (5.9%)	5 (4.0%)	29 (5.5%)	
Clopidogrel	45 (11.1%)	8 (6.5%)	53 (10.0%)	
Clopidogrel and Cardioaspirin	301 (74.3%)	95 (76.6%)	396 (74.9%)	
Other	26 (6.4%)	16 (12.9%)	42 (7.9%)	
EBPM	9 (2.2%)	0 (0.0%)	9 (1.7%)	
Statins				0.787 ³
N.missing data	380	63	443	
No	7 (4.9%)	10 (4.3%)	17 (4.6%)	
Yes	135 (95.1%)	221 (95.7%)	356 (95.4%)	
PCSK9 inhibitors				1.000 ⁴
N.missing data	380	63	443	
No	141 (99.3%)	230 (99.6%)	371 (99.5%)	
Yes	1 (0.7%)	1 (0.4%)	2 (0.5%)	
Ezetimibe				0.190 ³
N.missing data	380	63	443	
No	105 (73.9%)	156 (67.5%)	261 (70.0%)	
Yes	37 (26.1%)	75 (32.5%)	112 (30.0%)	
Inclisiran				

N.missing data	380	63	443	
No	142 (100.0%)	231 (100.0%)	373 (100.0%)	
Bempedoic acid				
N.missing data	380	63	443	
No	142 (100.0%)	231 (100.0%)	373 (100.0%)	

5.6.3 30-DAY RESULTS

About 30-day events, no cerebrovascular events registered in 358 patients (97.8%), 4 TIA/ amaurosis fugax, 2 minor strokes (ipsilateral), 2 major strokes (ipsilateral); 1 myocardial infarction (MI) and 2 deaths. (tab. V)

TABLE V 30-DAY RESULTS - 4. FISHER'S EXACT TEST

OUTCOMES	FS (N=522)	DL (N=294)	Total (N=816)	p.value
30-day cerebrovascular events				0.223 ⁴
N.missing data	357	93	450	
No	162 (98.2%)	196 (97.5%)	358 (97.8%)	
TIA / AMAUROSIS	1 (0.6%)	3 (1.5%)	4 (1.1%)	

Stroke minor	0 (0.0%)	2 (1.0%)	2 (0.5%)	
Stroke major	2 (1.2%)	0 (0.0%)	2 (0.5%)	
MI				1.000 ⁴
N.missing data	357	93	450	
No	165 (100.0%)	200 (99.5%)	365 (99.7%)	
Yes	0 (0.0%)	1 (0.5%)	1 (0.3%)	
30-day death				0.203 ⁴
N.missing data	357	93	450	
No	163 (98.8%)	201 (100.0%)	364 (99.5%)	
Yes	2 (1.2%)	0 (0.0%)	2 (0.5%)	

5.6.4 LONG-TERMS RESULTS

Overall follow-up was 0.0 - 9.6 (min-max), mean overall follow-up was 2.1 years (SD 1.9) and median overall follow-up 1.7 years (IQR 0.8, 2.5). Long-term results reported were: 5 strokes (0.8%), 9 TIA (1.4%), 4 MI (0.6%), 31 all-cause deaths (4.6%), 37 MACCE (5.9%), 21 restenosis (3.3%). About deaths reported, 27 events were for MACE. Among restenosis registered, 11 patients needed re-intervention (1.7%). We did not report for death for all causes, MACCE, death for MACCE any significative difference in groups separated for stent technology. Kaplan-Meier curves for stroke-free survival, overall-survival, MACE-free survival and restenosis-free survival, separated by gender respectively, show no statistical differences. Kaplan-Meier curves for stroke-free survival, overall-survival, MACCE-free survival and restenosis-free survival, separated by stent technology type, show no statistical differences.

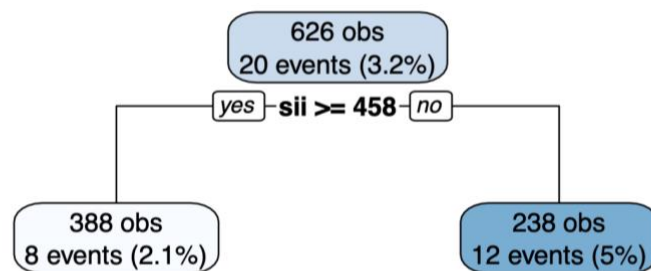
5.6.5 OUTCOMES SEPARATED BY SYSTEMIC IMMUNO-INFLAMMATION VALUES

The study of systemic immune-inflammation index (SII) in our population revealed a SII range between 24-15145.8 (min-max). We divided our population in three subgroups, according SII value:

- Less than 430.1 (N=270);
- 430.1 - 657.4 (N=273);
- Maior than 657.4 (N=272)

Our results show a statistical differences about association with ischemic heart disease appeared more frequent as the value decreased in SII tertiles. Kaplan-Meier curves separated for SII tertiles show no statistical differences for stroke-free survival, overall-survival, MACE-free survival and restenosis-free survival. Adopting recursive partitioning survival tree for restenosis time-to-event outcome using the SII as the sole splitting variable, we found a SII cut-off value of 458 (fig.4)

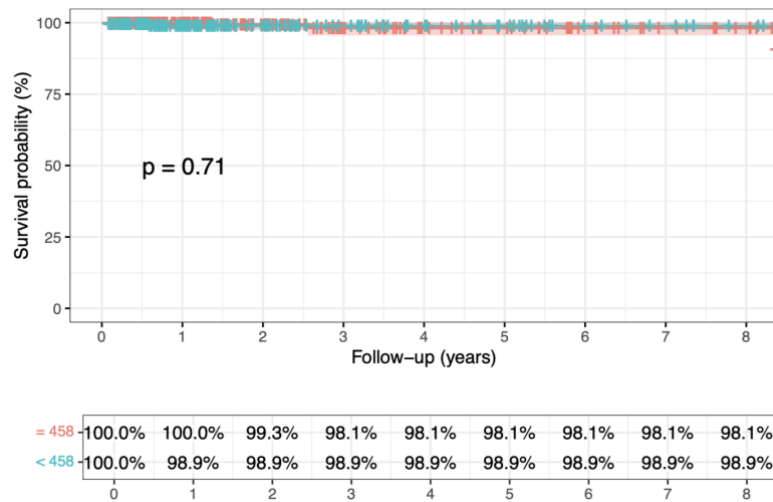
FIG.4 RECURSIVE PARTITIONING SURVIVAL TREE FOR RESTENOSIS TIME-TO-EVENT OUTCOME USING THE SII AS THE SOLE SPLITTING VARIABLE



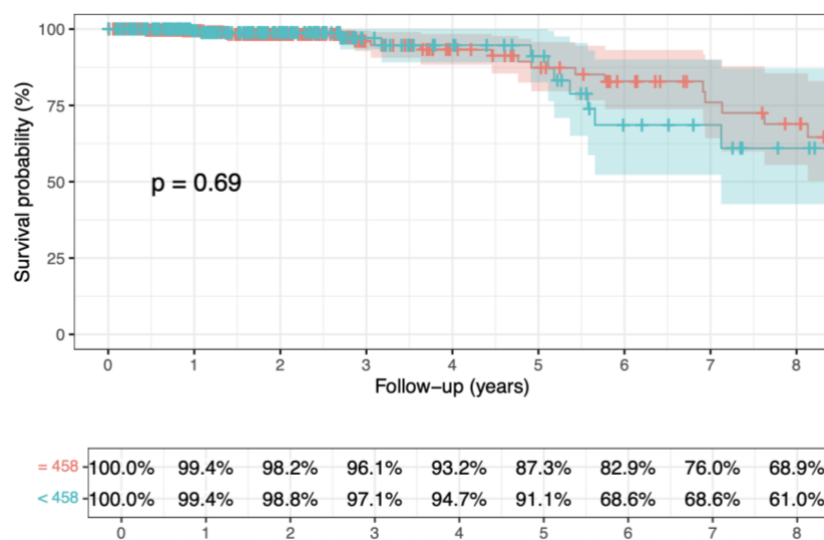
Kaplan-Meier curves separated for SII best cut-off (from survival tree) showed no statistically significative differences for stroke-free survival, overall-free survival, MACE-free survival but, interestingly, a p=0.017 for restenosis-free survival (Fig.5)

FIG. 5: KAPLAN-MEIER SURVIVAL CURVES, SEPARATED BY SII (BEST CUT-OFF FROM SURVIVAL TREE; P-VALUE FROM LOG-RANK TEST)

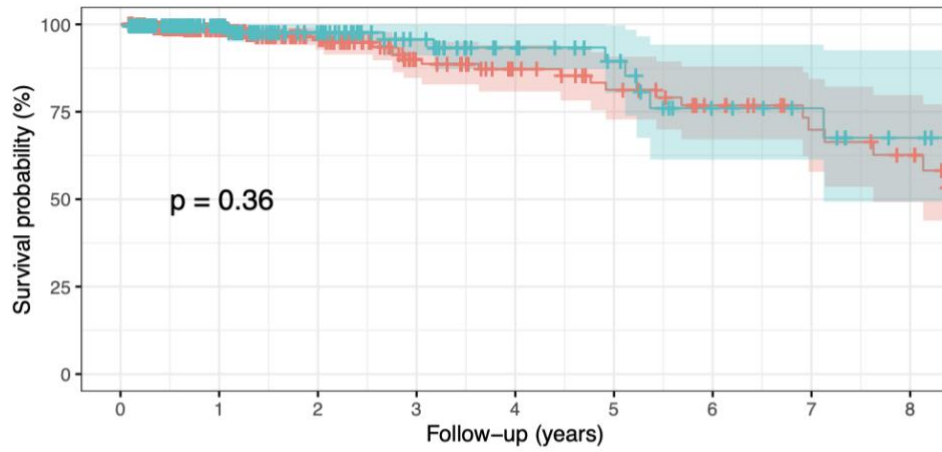
STROKE (IPSILATERAL)



DEATH

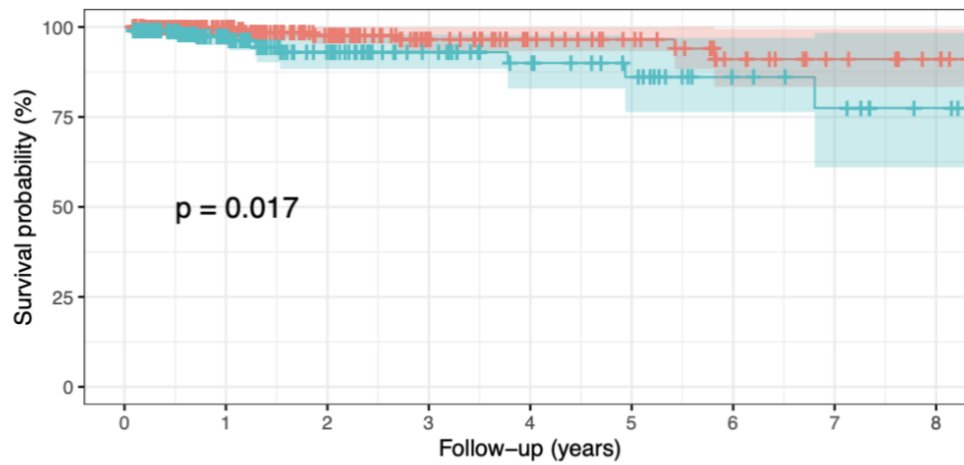


MACCE



= 458	100.0%	98.4%	95.7%	90.1%	87.2%	81.3%	76.8%	69.8%	62.7%
< 458	100.0%	99.6%	97.7%	95.7%	93.4%	89.5%	76.0%	76.0%	67.6%
	0	1	2	3	4	5	6	7	8

RESTENOSIS

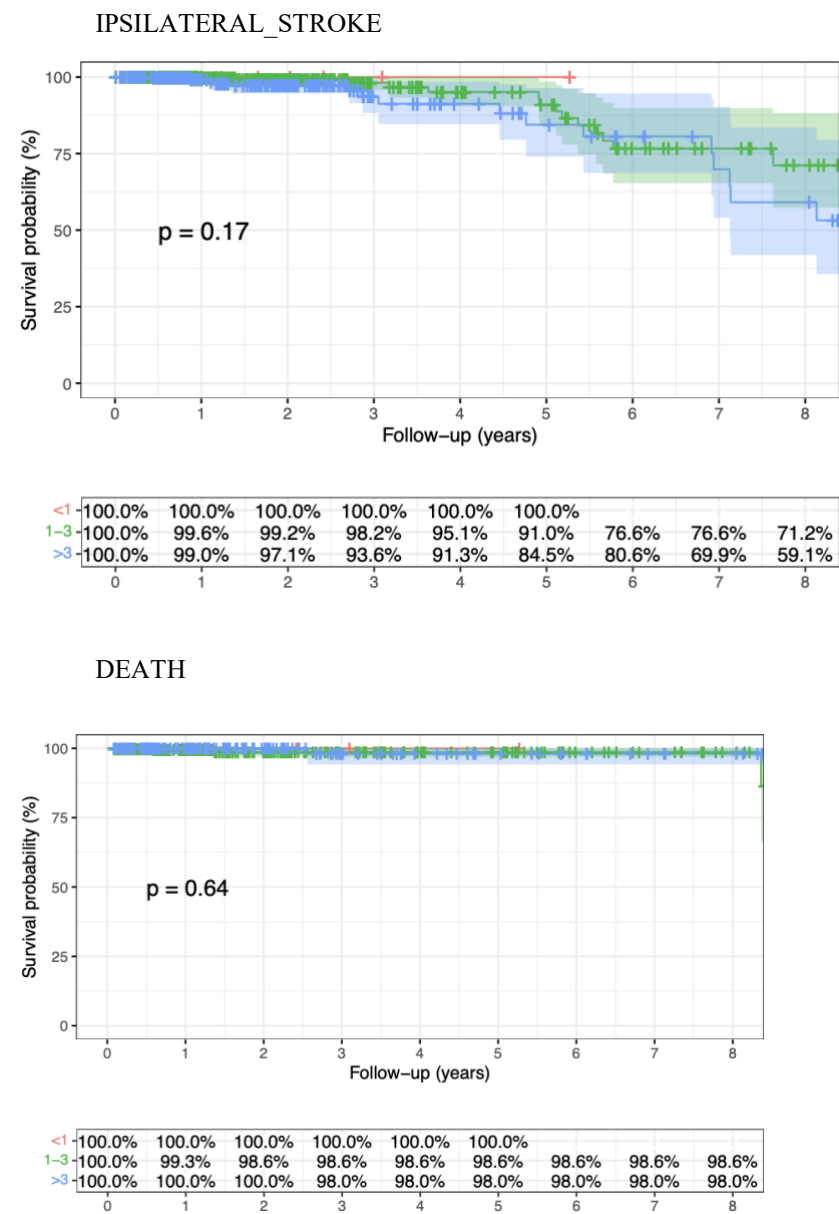


= 458	100.0%	99.7%	97.7%	96.5%	96.5%	96.5%	91.1%	91.1%	91.1%
< 458	100.0%	97.3%	93.0%	93.0%	90.0%	86.1%	86.1%	77.5%	77.5%
	0	1	2	3	4	5	6	7	8

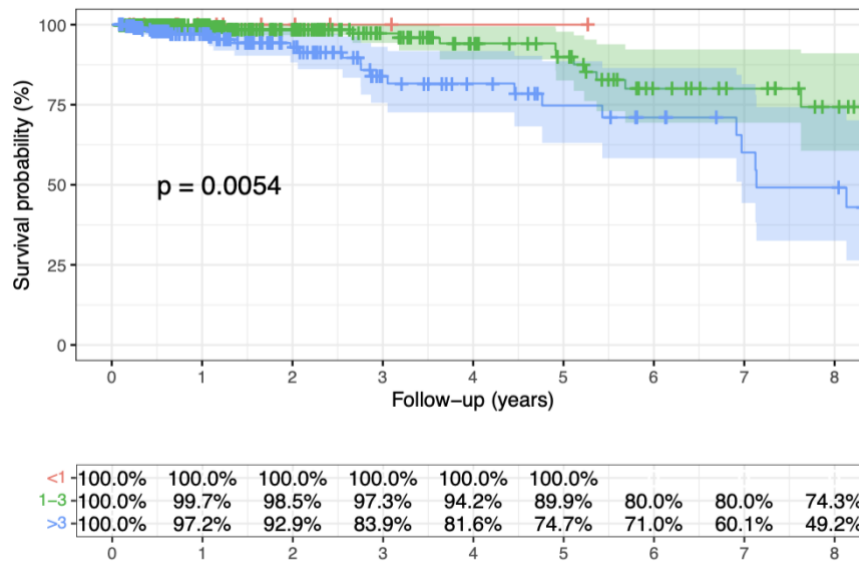
5.6.6 RESULTS SEPARATED BY NEUTROPHIL-TO-LYMPHOCYTE RATIO VALUES

Kaplan-Meier curves separated for clinical categories of neutrophil-to-lymphocyte ratio (NLR) showed no statistical significant differences for stroke-free survival, death-free survival and restenosis-free survival but merged a $p=0.05$ for MACE-free survival (Fig.6)

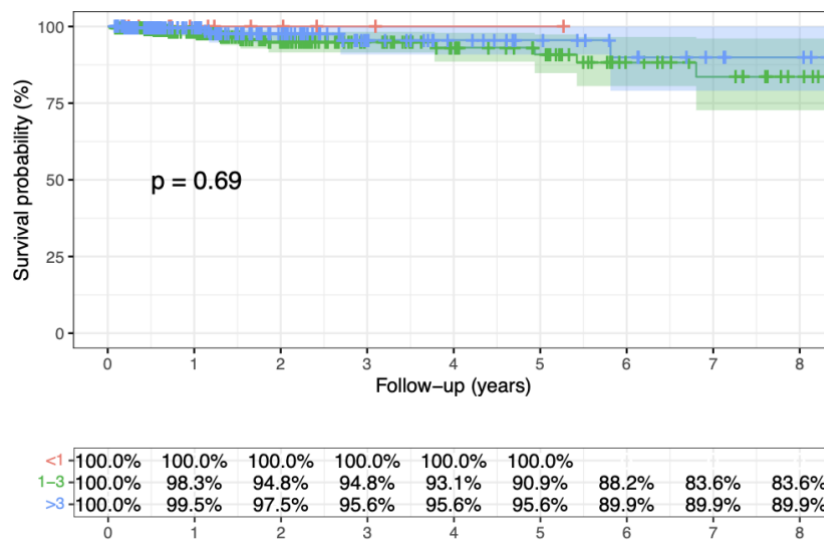
FIG. 6: KAPLAN-MEIER SURVIVAL CURVES, SEPARATED BY NLR (CLINICAL CATEGORIES; P-VALUE FROM LOG-RANK TEST)



MACCE



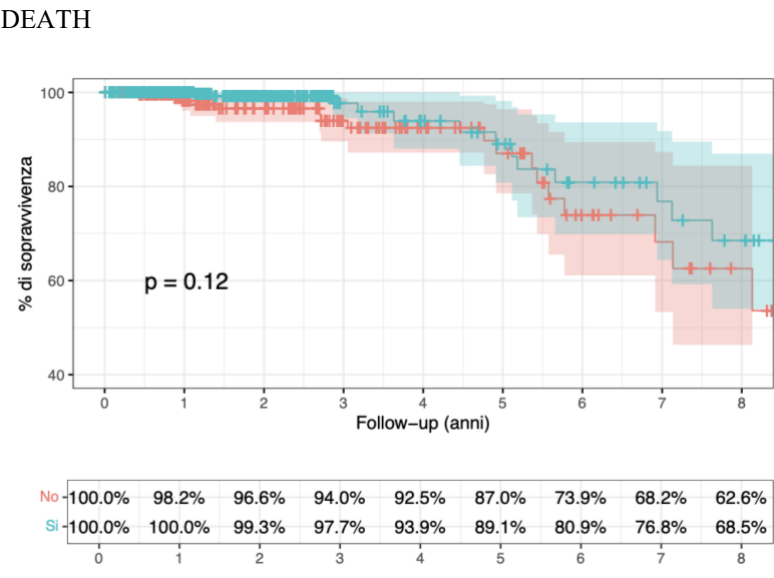
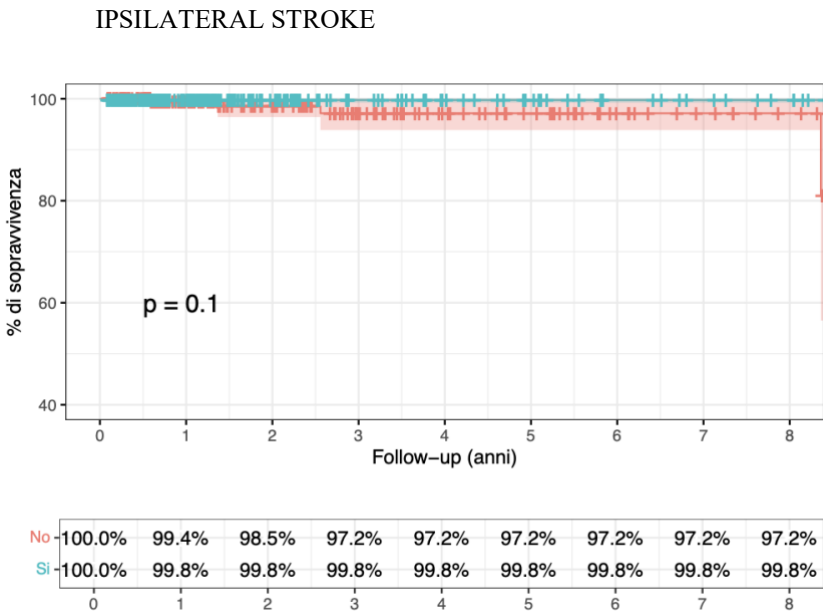
RESTENOSIS



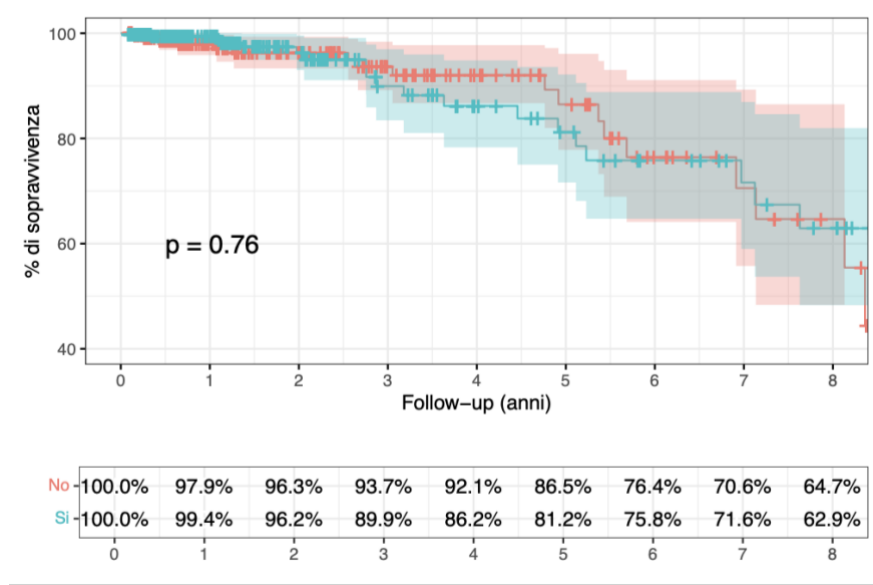
5.6.7 RESULTS FOR ASSOCIATION WITH DYSLIPIDEMIA

In addition, we analyzed Kaplan-Meier curve separated for dyslipidemia and we observed no statistical significant differences for stroke-free survival, death-free survival, MACCE-free survival and a $p=0.05$ for restenosis-free survival (fig. 7)

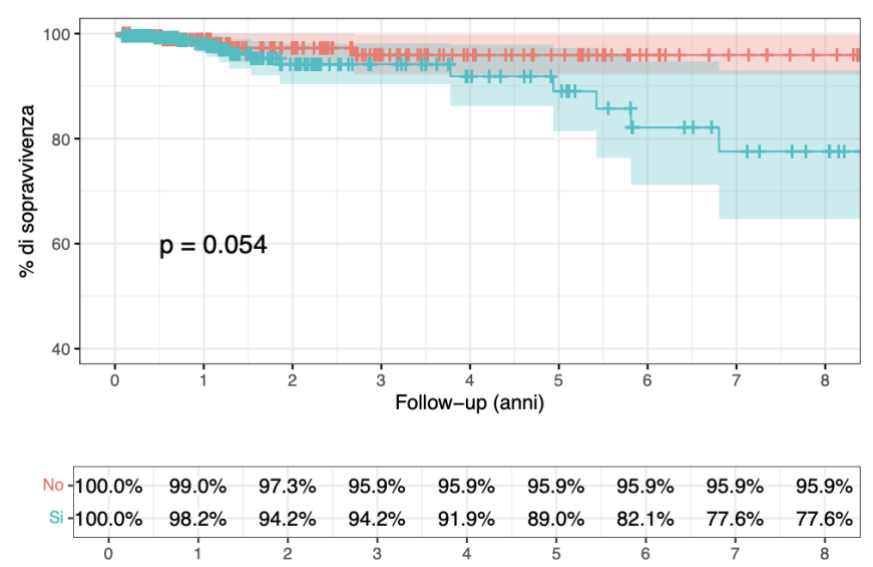
FIG 7: KAPLAN-MEIER SURVIVAL CURVES, SEPARATED BY DYSLIPIDEMIA



MACCE



RESTENOSIS



5.6.8 COX'S ANALYSIS

Results of univariable Cox models, separated by outcome and exposure group are reported in tab. VI

TABLE VI UNIVARIABLE COX MODEL, SEPARATED BY OUTCOME AND EXPOSURE GROUP

Objective	Group	Level	HR (95% CI)*	p-value
Stroke	Gender	Male vs. Female	1.20 (0.10-14.07)	0.883
	SII (tertiles)	430.1-657.4 vs. <430.1	0.78 (0.11-5.71)	0.809
	SII (tertiles)	>657.4 vs. <430.1	0.39 (0.03-4.49)	0.453
	SII (tree-based groups)	≥458 vs. <458	0.71 (0.11-4.46)	0.715
	Dyslipidemia	Yes vs. No	0.19 (0.02-1.74)	0.143
Death	Gender	Male vs. Female	1.48 (0.64-3.45)	0.361
	Stent type	DL vs. FG*	0.26 (0.03-2.05)	0.199
	SII tertiles	430.1-657.4 vs. <430.1	0.50 (0.19-1.28)	0.148
	SII tertiles	>657.4 vs. <430.1	1.02 (0.45-2.28)	0.967
	SII (tree-based groups)	≥458 vs. <458	0.86 (0.41-1.81)	0.686
MACCE	Dyslipidemia	Yes vs. No	0.57 (0.28-1.17)	0.127
	Gender	Male vs. Female	1.20 (0.58-2.49)	0.617
	Stent type	DL vs. FG*	0.41 (0.09-1.84)	0.244
	SII tertiles	430.1-657.4 vs. <430.1	0.92 (0.39-2.16)	0.844
	SII tertiles	>657.4 vs. <430.1	1.49 (0.67-3.29)	0.324
	SII (tree-based groups)	≥458 vs. <458	1.41 (0.68-2.91)	0.361

	Dyslipidemia	Yes vs. No	0.90 (0.47-1.73)	0.758
Restenosis	Gender	Male vs. Female	0.62 (0.26-1.48)	0.286
	Stent type	DL vs. FG*	0.97 (0.30-3.13)	0.964
	SII tertiles	430.1-657.4 vs. <430.1	0.76 (0.29-1.99)	0.577
	SII tertiles	>657.4 vs. <430.1	0.31 (0.08-1.14)	0.078
	SII (tree-based groups)	≥458 vs. <458	0.35 (0.14-0.86)	<u>0.022</u>
	Dyslipidemia	Yes vs. No	2.60 (0.95-7.14)	0.064

*HR: Hazard Ratio; CI: Confidence Interval; DL: Double-Layer; FG: First generation

Note: as no ipsilateral stroke events were recorded in patients with double-layer stents at the time of data analysis, no adjustment for stent type was made for this outcome.

Multivariable Cox models, adjusted for age at hospitalization, smoking, diabetes, stent technology type (first generation vs. double layer) and dyslipidemia (fully-adjusted models), reported, notably, a $p < 0.05$ for restenosis separated for tree based cutoff (HR 0.21, 0.07-0.64). (tab. VII) Multivariable sequentially-adjusted Cox models for restenosis (tab.VIII) showed a $p < 0.05$ for SII variable in each model for (≥ 458 vs. < 458) in each model. Discriminatory performance (Uno's C-statistic) of three sequentially-adjusted Cox models for predicting restenosis at three truncation times (1, 3 and 6 years), both before and after adding SII as an additional categorical covariate show (tab.IX)

TABLE VII MULTIVARIABLE FULLY-ADJUSTED COX MODELS, SEPARATED BY OUTCOME AND EXPOSURE GROUPS

Objective	Group	Level	HR (95% CI)*	p-value
Stroke	Gender	Male vs. Female	1.20 (0.10-14.07)	0.883

	SII (tertiles)	430.1-657.4 vs. <430.1	0.39 (0.03-4.90)	0.469
	SII (tertiles)	>657.4 vs. <430.1	0.36 (0.03-4.46)	0.430
	SII (tree-based groups)	≥458 vs. <458	0.47 (0.06-3.76)	0.474
Death	Gender	Male vs. Female	1.51 (0.54-4.26)	0.435
	SII tertiles	430.1-657.4 vs. <430.1	0.52 (0.19-1.44)	0.206
	SII tertiles	>657.4 vs. <430.1	1.00 (0.43-2.29)	0.995
	SII (tree-based groups)	≥458 vs. <458	0.87 (0.41-1.87)	0.726
MACCE	Gender	Male vs. Female	1.16 (0.48-2.78)	0.739
	SII tertiles	430.1-657.4 vs. <430.1	0.88 (0.35-2.21)	0.785
	SII tertiles	>657.4 vs. <430.1	1.21 (0.53-2.76)	0.647
	SII (tree-based groups)	≥458 vs. <458	1.25 (0.59-2.64)	0.565
Restenosis	Gender	Male vs. Female	0.61 (0.21-1.73)	0.348
	SII tertiles	430.1-657.4 vs. <430.1	0.49 (0.16-1.51)	0.215
	SII tertiles	>657.4 vs. <430.1	0.31 (0.08-1.19)	0.088

	SII (tree-based groups)	≥458 vs. <458	0.21 (0.07-0.64)	<u>0.006</u>
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*HR: Hazard Ratio; CI: Confidence Interval

The estimated HR was adjusted for age at hospitalization, smoking, diabetes, stent type (first generation vs. double layer) and dyslipidemia (fully-adjusted models).

Note: as no ipsilateral stroke events were recorded in patients with double-layer stents at the time of data analysis, no adjustment for stent type was made for this outcome.

TABLE VIII MULTIVARIABLE SEQUENTIALLY-ADJUSTED COX MODELS FOR RESTENOSIS

Model	Variables	HR (95% CI)*	p-value
Model 1	Age	0.98 (0.91-1.05)	0.484
	Gender (M vs. F)	0.50 (0.18-1.35)	0.170
	Smoke (Yes vs. No)	1.68 (0.51-5.51)	0.394
	Diabetes (Yes vs. No)	0.37 (0.11-1.17)	0.089
	SII (≥ 458 vs. < 458)	0.21 (0.07-0.63)	<u>0.005</u>
Model 2	Age	0.97 (0.90-1.04)	0.379
	Gender (M vs. F)	0.56 (0.21-1.52)	0.254

	Smoke (Yes vs. No)	1.51 (0.46-4.94)	0.495
	Diabetes (Yes vs. No)	0.41 (0.13-1.30)	0.129
	Dyslipidemia	2.34 (0.73-7.46)	0.152
	SII (≥ 458 vs. < 458)	0.21 (0.07-0.63)	<u>0.005</u>
Model 3	Age	0.97 (0.90-1.04)	0.367
	Gender (M vs. F)	0.55 (0.20-1.50)	0.247
	Smoke (Yes vs. No)	1.55 (0.47-5.09)	0.471
	Diabetes (Yes vs. No)	0.41 (0.13-1.29)	0.128
	Dyslipidemia	2.43 (0.75-7.88)	0.139
	Stent type	0.78 (0.22-2.71)	0.695
	SII (≥ 458 vs. < 458)	0.21 (0.07-0.63)	<u>0.006</u>

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*HR: Hazard Ratio; CI: Confidence Interval

TABLE IX UNO'S C-STATISTICS OF 3 SEQUENTIALLY-ADJUSTED COX MODELS FOR PREDICTING RESTENOSIS AT 3 TRUNCATION (1,3 AND 6 YEARS), BOTH BEFORE AND AFTER ADDING SII AS AN ADDITIONAL CATEGORICAL COVARIATE

Model	Truncation time (years)	C-statistic (95% CI)	p-value
Age + Sex + Smoke + Diabetes	1	0.72 (0.54 - 0.89)	0.169
Age + Sex + Smoke + Diabetes + SII (tree-based groups)	1	0.83 (0.64 - 1.01)	
Age + Sex + Smoke + Diabetes	3	0.63 (0.42 - 0.84)	0.072
Age + Sex + Smoke + Diabetes + SII (tree-based groups)	3	0.77 (0.57 - 0.96)	
Age + Sex + Smoke + Diabetes	6	0.72 (0.53 - 0.91)	0.482
Age + Sex + Smoke + Diabetes + SII (tree-based groups)	6	0.78 (0.63 - 0.92)	
Age + Sex + Smoke + Diabetes + Dyslipidemia	1	0.69 (0.50 - 0.87)	0.110
Age + Sex + Smoke + Diabetes + Dyslipidemia + SII (tree-based groups)	1	0.80 (0.60 - 1.00)	
Age + Sex + Smoke + Diabetes + Dyslipidemia	3	0.63 (0.42 - 0.85)	0.071
Age + Sex + Smoke + Diabetes + Dyslipidemia + SII (tree-based groups)	3	0.76 (0.56 - 0.96)	
Age + Sex + Smoke + Diabetes + Dyslipidemia	6	0.76 (0.55 - 0.96)	0.462
Age + Sex + Smoke + Diabetes + Dyslipidemia + SII (tree-based groups)	6	0.81 (0.65 - 0.97)	
Age + Sex + Smoke + Diabetes + Dyslipidemia + Stent type	1	0.68 (0.49 - 0.87)	0.146
Age + Sex + Smoke + Diabetes + Dyslipidemia + Stent type + SII (tree-based groups)	1	0.80 (0.60 - 1.00)	
Age + Sex + Smoke + Diabetes + Dyslipidemia + Stent type	3	0.63 (0.41 - 0.85)	0.089
Age + Sex + Smoke + Diabetes + Dyslipidemia + Stent type + SII (tree-based groups)	3	0.76 (0.56 - 0.96)	
Age + Sex + Smoke + Diabetes + Dyslipidemia + Stent type	6	0.76 (0.56 - 0.96)	0.405
Age + Sex + Smoke + Diabetes + Dyslipidemia + Stent type + SII (tree-based groups)	6	0.81 (0.65 - 0.97)	

CI: Confidence Interval, obtained by perturbation-resampling method (1000 resampling); p-value from z-test for comparing the difference in C-statistics between two nested models

5.7 DISCUSSIONS

In our cohorts we registered a 30-day stroke rate of 1%, that is lower than 4.1% of CREST-1 trial [16], in which patients with symptomatic or asymptomatic carotid stenosis were randomly assigned to undergo carotid-artery stenting (with only FGS) or carotid endarterectomy. Indeed in our patients grouped by stent type, we observed in FGS group 1 TIA/Amaurosis (0.6%), no minor strokes, 2 major strokes (1.2%); in DL group we observed 3 TIA/amaurosis (1.5%), 2 minor strokes in DL group (1%) and no major strokes. No statistical differences merged about 30-day stroke rate between FGS and DL. Possibly differences derive from:

- a highly selected population based on anatomical features and plaque's characteristics;[162][38]
- the use of a standardized technical protocol strictly applied by experienced operators (more than 6 procedures/year and a lifetime experience of at least 25 transfemoral CAS procedures)
- employment of EPDs probably allowed to minimize the risk of adverse events during the procedure (in 99.6% of patients).

Long-term stroke rate in our study population is 0.8%, with all stroke events in FGS group. Kaplan-Meier curve for ipsilateral stroke-free survival analysis do not show any statistically significant difference in groups separated by stent technology (FGS vs DL) and gender. About cardiovascular events, we registered peri-operative myocardial infarction in DL group (0.5%, global rate 0.3%). Long-term MACCE showed a

significant static difference between FGS and DL, reporting a global rate of 5.9% (FGS 9.4% Vs DL 0.8%). This result is in line with the larger meta-analyses [119][147] (see cf. chapter 4). On the other hand, this difference was not evident in Kaplan-Meier curve for MACE-free survival in our study. We registered 2 all-cause deaths (0.5%) in the peri-operative period, all in FGS group (1.2%). These findings confirm what recently merged from CATALISMA registry [138] (see cf. Chapter 2). In addition, our 30-day myocardial infarction and 30-day death results, respectively, seem to be slightly lower than CREST-1[16] results (30-day myocardial infarction rate 1.1% and 30-day death rate 0.7%). We observed a lower incidence of ISR in new generation stent group (4.5% for FGS and 1.6% for DL group, respectively, $p=0.043$). Considering the large prevalence of Roadsaver stent in DL group, this result seems to be in partial opposition with result of recent meta-analysis of Mazurek et al. [119], suggesting a dual-layer class-effect from real-world experience in reducing ISR restenosis rate in comparison with FGS from real-world experience. Long-term results from Kaplan-Meier curves do not show any significant statistical difference in group separated by stent technology and gender.

About predictive role of SII biomarker, we observed in tertiles in our study population a significant statistical difference in patient's history for peripheral artery disease ($p=0.04$) and antiplatelet therapy ($p=0.041$) with a prevalence of dual-antiplatelet therapy in patients with a lower value of pre-operative SII. Recursive partitioning survival tree for time-to-event outcome using the SII as the sole splitting variable, show us for ISR-free survival a significant statistical difference, with more events in patients with a lower value of SII (≤ 458). This result is confirmed by univariable Cox-model for ISR and by multivariable fully adjusted Cox models for age at hospitalization, smoking, diabetes, stent type (first generation vs. double layer) and dyslipidemia (HR 0.21, 0.07-0.64). This finding differs from what reported in Literature[82][89]: it has been reported that elevated levels of neutrophils and platelets together, along with reduced levels of lymphocytes, are associated with vascular disease[163][164]. Using Uno's C-statistic of three sequentially adjusted Cox models for predicting restenosis at three truncation times (1, 3 and 6 years), both before and after adding SII as an additional categorical covariate, did not merge any statistical difference. Discriminatory performance (Uno's C-statistic) of three sequentially adjusted Cox models for predicting restenosis at three truncation times (1, 3 and 6 years), both before and after adding SII as an additional categorical covariate, no statistical differences merge.

We analyzed our study population separating outcome for dyslipidemia in consideration of proatherosclerotic role of hyperlipidemia and oxidative damage, can trigger systemic inflammation.[90] This inflammation is currently regarded as the core mechanism of atherosclerotic formation.[73] It leads to release of pro-inflammatory cytokines, resulting in an increased neutrophil count.[90] In addition, we analyzed inflammation role in our study population calculating also the role of neutrophil-to-lymphocytes ratio (NLR, neutrophils count/ lymphocytes count). Separating study population in NLR categories (established from population values), we observe in Kaplan-Meier curves a significant statistical

difference in MACE-free survival ($p<0.05$), with lower survival in patients in category $NLR>3$. This result is in line with a recent meta-analysis of Kurniawan et al. [72]. High NLR is reported being associated with vulnerable carotid plaque[165]. Differently from recent Siahaan et al.[91] meta-analysis, NLR do not show any correlation with the risk or ISR in our study.

Our study has some limitations:

- there are not included inflammatory markers such as CRP, interleukin-6 or thromboxane A2;
- it's a retrospective observational study;
- stent selection was left to the operators' decision and there is not a standardized algorithm for the choice;
- proportion of missing data;
- differences in three centers population dimension.

In addition Previous studies also reported that dehydration and overhydration may influence the NLR [166] and SII as consequence.[167] We did not evaluate the effects of these factors in this study.

5.8 CONCLUSIONS

Di.Ge.STENT.IIS study shows a 30-day cerebrovascular event rate: 2.2% (TIA/amaurosis 1.1%, stroke minor 0.5%, stroke major 0.5%), a 30-day, MI rate: 0.3%, a 30-day all-cause-death rate: 0.5% (7.4 in FGS vs 0.4% in DL, $p<0.001$); long-term outcomes were: Ipsilateral stroke rate: 0.8%, MACCE-rate: 5.9% (9.4% in FGS Vs 0.8 in DL, $p=0.001$), all-cause-death rate: 4.6% and ISR 3.3% (4.5 in FGS Vs 1.6% in DL, $p=0.043$). No Gender-related differences merged in our study. In our study population, when SII value is adjusted for confounding factors, no statistical differences are evident. Multi-centers, larger, perspective and controlled studies are needed to confirm results about new generation carotid stents and the possible predictive role of SII in CAS.

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