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PERIPHERAL

# 1-Year Results From a Prospective Experience on CAS Using the CGuard Stent System

## The IRONGUARD 2 Study

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## ABSTRACT

**OBJECTIVES** The aim of this study was to evaluate the 1-year safety and efficacy of a dual-layered stent (DLS) for carotid artery stenting (CAS) in a multicenter registry.

**BACKGROUND** DLS have been proved to be safe and efficient during short-term follow-up. Recent data have raised the concern that the benefit of CAS performed with using a DLS may be hampered by a higher restenosis rate at 1 year.

**METHODS** From January 2017 to June 2019, a physician-initiated, prospective, multispecialty registry enrolled 733 consecutive patients undergoing CAS using the CGuard embolic prevention system at 20 centers. The primary endpoint was the occurrence of death and stroke at 1 year. Secondary endpoints were 1-year rates of transient ischemic attack, acute myocardial infarction, internal carotid artery (ICA) restenosis, in-stent thrombosis, and external carotid artery occlusion.

**RESULTS** At 1 year, follow-up was available in 726 patients (99.04%). Beyond 30 days postprocedure, 1 minor stroke (0.13%), four transient ischemic attacks (0.55%), 2 fatal acute myocardial infarctions (0.27%), and 6 noncardiac deaths (1.10%) occurred. On duplex ultrasound examination, ICA restenosis was found in 6 patients (0.82%): 2 total occlusions and 4 in-stent restenoses. No predictors of target ICA restenosis and/or occlusion could be detected, and dual-antiplatelet therapy duration (90 days vs 30 days) was not found to be related to major adverse cardiovascular event or restenosis occurrence.

**CONCLUSIONS** This real-world registry suggests that DLS use in clinical practice is safe and associated with minimal occurrence of adverse neurologic events up to 12-month follow-up. (J Am Coll Cardiol Intv 2021;14:1917–1923)


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**ABBREVIATIONS AND ACRONYMS**

**AMI** = acute myocardial infarction

**CAS** = carotid artery stenting

**DAPT** = dual-antiplatelet therapy

**DLS** = dual-layered stent(s)

**ECA** = external carotid artery

**EPD** = Embolic Protection Device

**ICA** = internal carotid artery

**MACE** = major adverse cardiovascular event(s)

**NIHSS** = National Institutes of Health Stroke Scale

**TIA** = transient ischemic attack

Carotid artery stenting (CAS) has emerged as a valid alternative to carotid endarterectomy in both symptomatic and asymptomatic patients requiring extracranial internal carotid artery (ICA) revascularization (1).

However, plaque protrusion through the stent struts seems to be related to periprocedural ipsilateral strokes, negatively affecting clinical outcomes of CAS with conventional stents because of the risk for cerebral embolization causing ipsilateral periprocedural new strokes. Dual-layered stents (DLS) (2-4), a new generation of devices, were recently developed to overcome this adverse procedural occurrence, consisting of Nitinol stents combined with a mesh (Nitinol or polyethylene terephthalate) that potentially captures plaque debris and thrombus between the stent and the arterial wall (5).

Several small studies (6-9) and a patient-based meta-analysis (10) have reported more than satisfactory safety and clinical efficacy at 30 days. At 12-month follow-up, a wide range of restenosis rates emerged among different DLS-based studies and different DLS devices (11).

The aim of this study was to assess the clinical efficacy of the CGuard DLS (Inspire MD) with respect to death, stroke, and in-stent restenosis at 12-month follow-up from a real-world, large prospective Italian study.

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## METHODS

**STUDY DESIGN.** From January 2017 to June 2019, 20 Italian centers prospectively enrolled patients undergoing CAS using a specific DLS, the CGuard embolic prevention system (12). The present study conformed to the Declaration of Helsinki, and ethics committees were notified. All patients enrolled in the study gave written informed consent to undergo CAS and be included in the study. For each patient, data were anonymized and collected in a dedicated web-based database.

**STUDY POPULATION.** Inclusion criteria considered the degree of stenosis and related symptoms: symptomatic stenosis of the ICA ≥50%, asymptomatic stenosis ≥80%, and life expectancy >5 years. Exclusion criteria were target ICA reference diameter smaller than 3 mm or larger than 9 mm, history of previous life-threatening contrast media reaction, contraindications to aspirin and clopidogrel, known allergy to nickel or titanium, uncorrectable bleeding disorders, evidence or previous (<12 months) intracranial hemorrhage or brain surgery, history of intracerebral aneurysms or arteriovenous malformation, common carotid artery ostial lesions (unless untreated simultaneously with index CAS), occlusion of target vessels, intraluminal thrombosis, previously stented target carotid artery, and inability to comply with enrollment and follow-up requirements.

All CAS procedures considered in the present analysis were performed according to each operating unit's therapeutic standard and devices' specific instructions for use (12).

**CONCOMITANT THERAPY.** All patients received dual-antiplatelet therapy (DAPT) at a standard dose for at least 2 days before the CAS procedure (alternatively, intraprocedural 600-mg clopidogrel loading was performed). For intraprocedural anticoagulation, unfractionated heparin (70-100 IU/kg) was administered to maintain an activated clotting time >250 seconds. After the procedure, DAPT, including aspirin and clopidogrel, was continued for at least 1 month. After the first month postprocedure, clopidogrel was discontinued according to each enrolling institution's clinical protocol, while aspirin was continued indefinitely.

**PATIENT FOLLOW-UP.** Following hospital discharge, participants were clinically assessed at 30 days and 12 months per protocol; unplanned visits were also recorded, if available. At each visit, carotid duplex ultrasound, neurologic assessment, physical examination, and adverse event recording were routinely conducted.

**ENDPOINTS.** The primary endpoint was the occurrence of death and stroke at 1 year; secondary endpoints were 1-year rates of transient ischemic attack (TIA), acute myocardial infarction (AMI), restenosis, in-stent thrombosis, and external carotid artery (ECA) occlusion.

Major adverse cardiovascular events (MACE) were defined as death, stroke, and AMI.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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At each institution, a neurologist or a National Institutes of Health Stroke Scale (NIHSS)-certified physician evaluated all patients during hospitalization and following an event that occurred during follow-up.

Neurologic complications were classified as follows: 1) TIA was defined as a new transient episode of neurologic dysfunction caused by focal brain or retinal ischemia without imaging evidence of acute infarction; 2) minor stroke was defined as a new neurologic deficit that entirely resolved in 30 days or increased the NIHSS score by ≤3 points compared with the preprocedural evaluation; and 3) major stroke was defined as a new neurologic deficit that persisted for >30 days and increased the NIHSS score by ≥4 points compared with the preprocedural evaluation.

Restenosis was defined as either the detection of stenosis of 50% to 99% or occlusion on ultrasonographic examination performed after stenting, with the degree of stenosis determined according to the norms of the local ultrasonography laboratory (12). Patients with restenosis between 70% and 99% underwent new endovascular procedures.

**STATISTICAL ANALYSIS.** Data on demographic characteristics, preprocedural computed tomographic angiographic evaluation, and intraprocedural details were entered into a prospectively compiled web-based database and further analyzed as potential risk factors for postprocedural outcomes. Continuous variables are expressed as mean ± SD and were compared using paired or unpaired Student's *t*-tests. Categorical variables are expressed as counts and percentages and were compared using the Fisher exact test or the chi-square test. Odds ratios and risk ratios to study the primary endpoint were calculated for clinical and procedural variables. A 2-sided *P* value of <0.05 was considered to indicate statistical significance. Long-term outcomes were determined using Kaplan-Meier curves and log-rank tests. All analyses were performed using SPSS version 23.0 (IBM).

## RESULTS

Demographic and procedural characteristics of the study population have been previously published (12). Demographic, anatomical, and procedural characteristics of enrolled patients are reported in **Table 1**.

As previously reported, up to 30 days from discharge, 4 strokes (1 fatal and 3 minor) and 1 death were recorded. Intraprocedural ECA occlusion occurred in 8 patients (1.09%) (12).

DAPT was maintained in all patients till the 30th postoperative day per protocol and till the 90th day in 295 patients (40.63%) according to each institution's clinical practice.

One-year data were available for 726 out the 733 initially treated patients, for a rate of loss to follow-up of 0.95%.

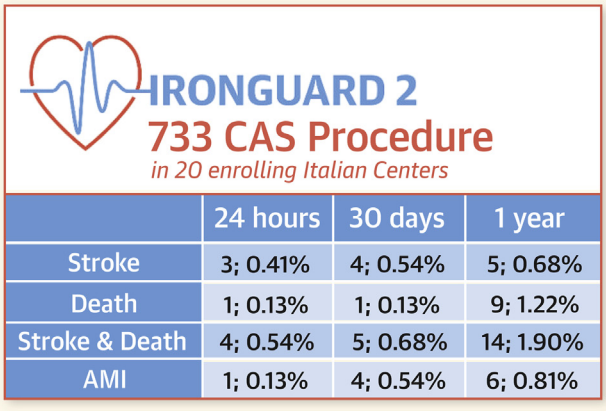
From day 31 to day 365, the rate of any ipsilateral stroke was 0.13%, while new cerebral adverse events

**TABLE 1 Demographic, Anatomical, and Procedural Characteristics of Patients Included in the Registry**

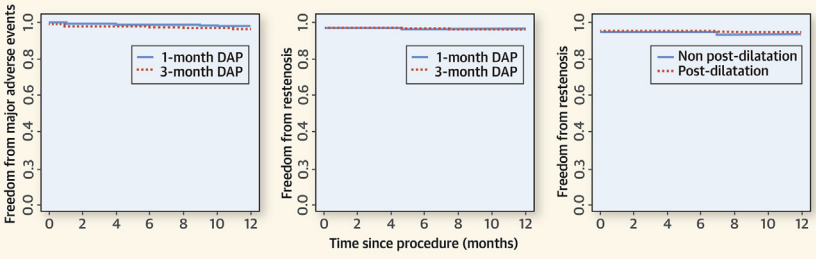
| | |
|---|---|
| Age, y | 73.03 ± 7.84 (39-97) |
| Male | 516 (70.39) |
| Octogenarians | 141 (19.23) |
| High risk | 386 (52.66) |
| Symptomatic stenosis | 131 (17.87) |
| Hypertension | 622 (84.85) |
| Diabetes | 264 (36.01) |
| Dyslipidemia | 552 (75.30) |
| Smoking history | 429 (58.52) |
| CAD history | 278 (37.92) |
| Right-side internal carotid artery | 395 (53.81) |
| Plaque | |
| Hyperechoic | 163 (22.23) |
| Isoechoic | 107 (14.59) |
| Hypoanechoic | 181 (24.69) |
| Dishomogenous | 172 (23.46) |
| Ulcerated | 40 (5.45) |
| Thin fibrous cap | 29 (3.99) |
| Post-CEA restenosis | 41 (5.59) |
| Aortic arch | |
| Type I | 369 (50.34) |
| Type II | 268 (36.56) |
| Type III | 39 (5.32) |
| Bovine | 57 (7.78) |
| Tortuosity | |
| None | 194 (26.46) |
| Low | 289 (39.42) |
| Moderate | 191 (26.05) |
| Severe | 59 (8.07) |
| Severe calcification | 199 (27.14) |
| Severe thrombosis | 147 (20.05) |
| Femoral access | 713 (97.27) |
| Any protection system | 731 (99.72) |
| Proximal protection | 138 (18.82) |
| Predilatation | 169 (23.05) |
| Postdilatation | 607 (82.81) |

Values are mean ± SD (range) or n (%).
CAD = coronary artery disease; CEA = carotid endarterectomy.

**CENTRAL ILLUSTRATION** **Event Rates in the IRONGUARD 2 Study**




| | 24 hours | 30 days | 1 year |
|---|---|---|---|
| Stroke | 3; 0.41% | 4; 0.54% | 5; 0.68% |
| Death | 1; 0.13% | 1; 0.13% | 9; 1.22% |
| Stroke & Death | 4; 0.54% | 5; 0.68% | 14; 1.90% |
| AMI | 1; 0.13% | 4; 0.54% | 6; 0.81% |




| | | Incidence without the variable N (%) | Incidence with the variable N (%) | *P* (OR; 95% CI) |
|---|---|---|---|---|
| Hypertension | | 0 (0) | 5 (0.80) | 0.34 (NA) |
| Diabetes | | 2 (0.42) | 3 (1.13) | 0.26 (2.68; 0.44-16.16) |
| Dyslipidaemia | | 1 (0.55) | 4 (0.72) | 0.80 (1.31; 0.14-11.83) |
| Smoking history | | 3 (0.98) | 2 (0.46) | 0.41 (0.48; 0.08-2.91) |
| Coronary artery disease | | 3 (0.65) | 2 (0.71) | 0.92 (1.09; 0.18-6.57) |
| Octogenarians | | 3 (0.51) | 2 (1.41) | 0.23 (2.82; 0.46-17.06) |
| High clinical risk | | 2 (0.59) | 2 (0.50) | 0.49 (0.53; 0.08-3.25) |
| Symptomatic stenosis | | 3 (0.49) | 2 (1.52) | 0.19 (3.09; 0.51-18.71) |
| Plaque | Hyperechoic | 4 (0.70) | 1 (0.61) | 1.00 (NA) |
| | Isoechoic | 3 (0.47) | 2 (1.89) | |
| | Hypo-anechoic | 4 (0.72) | 1 (0.55) | |
| | Disomogeneous | 5 (0.89) | 0 (0) | |
| | Ulcerated | 4 (0.57) | 1 (2.5) | |
| | Thin fibrous cap | 5 (0.71) | 0 (0) | |
| | Post-CEA restenosis | 5 (0.72) | 0 (0) | |
| | Unstable | 4 (0.60) | 1 (1.44) | 0.41 (2.42; 0.26-22.01) |
| Aortic arch | Type I | 2 (0.54) | 3 (0.81) | 1.00 (NA) |
| | Type II | 3 (0.64) | 2 (0.74) | |
| | Type III | 5 (0.72) | 0 (0) | |
| | Bovine | 5 (0.73) | 0 (0) | |
| Tortuosity | None | 4 (0.74) | 1 (0.51) | 1.00 (NA) |
| | Low | 2 (0.45) | 3 (1.03) | |
| | Moderate | 4 (0.73) | 1 (0.52) | |
| | Severe | 5 (0.74) | 0 (0) | |
| | Significant | 4 (0.82) | 1 (0.40) | 0.50 (0.48; 0.05-4.32) |
| Severe calcification | | 3 (0.56) | 2 (1.00) | 0.51 (1.79; 0.29-10.83) |
| Severe thrombosis | | 3 (0.51) | 1 (0.68) | 0.99 (0.99; 0.11-8.98) |
| Distal protection | | 1 (0.71) | 4 (0.67) | 0.76 (0.70; 0.07-6.84) |
| Predilatation | | 4 (0.70) | 1 (0.59) | 0.80 (0.83; 0.09-7.50) |
| Postdilatation | | 1 (0.80) | 4 (0.65) | 0.86 (1.20; 013-10.88) |

**Sirignano, P. et al. J Am Coll Cardiol Intv. 2021;14(17):1917–1923.**

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were registered in 5 patients: 1 minor stroke and 4 TIAs (0.55%).

Cumulatively, 8 patients (1.10%) died between postoperative days 31 and 365: 4 malignancies (0.55%), 1 suicide (0.13%), 1 undefined complication of Guillain-Barré syndrome (0.13%), and 2 fatal AMIs (0.27%).

Consequently, the 365-day cumulative stroke rate was 0.68%; immediate (24 hours), 30-day, and 1-year rates of stroke, death, stroke and death, and AMI are depicted in the **Central Illustration**.

On duplex ultrasound examination, ICA restenosis was found in 6 patients (0.82%): 2 occlusions left untreated because of unknown time of onset, and 4 asymptomatic in-stent restenoses (2 of which, evaluated as >70% and presenting peak systolic velocity >450 cm/s, were successfully treated by CAS). New computed tomographic angiography was performed only in those patients requiring reintervention. No additional ECA was found to be occluded during follow-up, thus the ECA patency rate at 1 year was 98.8% (718 of 726).

On univariate analysis, none of the clinical, anatomical, or procedural characteristics were found to be statistically related to new stroke occurrence during the entire study period (**Central Illustration**).

On log-rank analysis, DAPT duration was not found to be related to MACE ($P = 0.17$) (**Central Illustration**) or restenosis occurrence ($P = 0.62$) (**Central Illustration**); furthermore, rate of freedom from restenosis was not affected by the intraoperative performance of stent postdilatation ($P = 0.97$) (**Central Illustration**).

## DISCUSSION

This study demonstrates that: 1) in a real-world evaluation of CAS, DLS were safely used for guideline-based treatment of symptomatic or asymptomatic extracranial carotid artery stenosis, with low rates of MACE and restenosis at 12 months; 2) prolongation of DAPT beyond 30 days (up to 90 days) postprocedure does not seem to reduce MACE or restenosis rate; and 3) intraprocedural postdilation does not affect restenosis rate at 1 year.

IRONGUARD 2 represents, to date, the largest prospective multicenter multispecialty registry on the use of mesh-covered stents. More than 700 consecutive CAS patients were enrolled during the study period, treated using the CGuard DLS, and followed for 12 months. All centers have established experience with the new stent system, as previously reported in detail (12).

Although it is well known that the majority of cerebral adverse events after CAS occur in the first 30 postprocedural days, it cannot be denied that risk still exists beyond the first month. Data from previously published studies on different DLS (6-9) showed a low but significant risk for new stroke occurrence between postoperative days 30 and 365. A patient-level showed 6 minor strokes (1.08%) during hospitalization, 1 ipsilateral stroke between hospital discharge and 30 days, and 4 additional strokes (0.71%) by the end of 1-year follow-up (11). The present experience, reporting results on patients treated with only a single DLS implantation, showed even better performance during the 1-year period: 3 strokes (1 fatal [0.41%]) were registered at hospital discharge, 1 at 1 month, and an additional stroke at 12 months, the latter 2 strokes both minor. Overall, the meta-analysis accounted for 10 strokes (1.79%) during the entire 12-month observation period (11), while our multicenter experience cumulatively registered 5 strokes (0.68%), confirming the more than satisfactory results achievable in an unselected patient population. However, these satisfactory results are related to a series of nonrandomized patients, mostly treated for severe asymptomatic stenosis; this could partially justify the good rate of adverse neurologic events reported.

None of the clinical, anatomical, or technical preoperative or intraoperative characteristics analyzed were statistically associated with stroke occurrence during the entire study period; this

**CENTRAL ILLUSTRATION Continued**

**(Top left)** 24-hour, 30-day, and 1-year rates of stroke, death, stroke and death, and acute myocardial infarction. **(Bottom left)** Kaplan-Meier estimates of freedom from major adverse events in patients who received 30- or 90-day dual-antiplatelet therapy (DAPT), freedom from restenosis in patients who received 30- or 90-day DAPT, and freedom from restenosis in patients submitted or not to intraprocedural postdilatation **(Right)** Clinical, anatomical, and procedural characteristics potentially affecting stroke occurrence during the entire study period. CEA = carotid endarterectomy; DAP = dual-antiplatelet therapy; NA = not available.

finding is particularly important because the use of this device minimizes the risk related to the treatment of symptomatic patients. Although these results seem encouraging, they should be interpreted with caution given the relatively small percentage of symptomatic patients in the study (131 of 733 [7.87%]), even if compared with data reported from other similar studies (6-9).

Despite the widespread adoption of CAS procedures, the duration of postoperative DAPT after DLS implantation (11) is still unclear. As suggested by the available guidelines, every patient who undergoes CAS, regardless the type of implanted stent, should receive DAPT throughout the 30-day perioperative period. After that, no additional benefit of DAPT over antiplatelet monotherapy is reported. However, those recommendations were based largely on the coronary research because of the lack of data from large trials in CAS patients, especially with the new-generation DLS (13). In particular, no data on a comparison between DAPT and antiplatelet monotherapy, beyond the 30-day perioperative period, have ever been reported.

Recently, reported datasets have specifically investigated the possible correlation existing between DLS implantation, DAPT, and stent thrombosis, demonstrating a significantly lower rate of thrombosis in subjects who underwent prolonged (3-month) DAPT (14,15). However, those data were derived from experiences performed in emergently treated patients, mostly using DLS other from the CGuard embolic prevention system. Indeed, in this study, no stent thrombosis occurred during the first postoperative month, and only 2 occlusive restenoses were detected at 12-month follow-up. When dividing the patient population into 2 groups according to DAPT duration (30 or 90 days), no difference in freedom from cardiovascular adverse events at 1 year could be detected. This finding is in contrast to the conclusion of a recent meta-analysis (16) and does not support the need to prolong DAPT beyond 30 days after CAS with a DLS. Such data should be considered hypothesis generating for future investigational studies.

In this registry, DLS use was associated with a low rate (<1%) of restenosis, and the lack postdilatation was not associated with a higher occurrence of restenosis during follow-up. In consideration of this observation, stent postdilatation should not be considered a mandatory part of a CAS procedure using this new-generation device.

**STUDY LIMITATIONS.** The main limitation was in the design of the study, a prospective registry, which was not randomized and did not allow us to compare the results with a control patient population.

Moreover, per study protocol, no centralized core laboratory analysis of ultrasound images was performed, and degree of stenosis was determined by the standards of the local ultrasonography laboratory. Although all evaluations were performed by highly skilled operators, potential interpretation bias in defining the exact restenosis degree could not be absolutely excluded.

Clopidogrel response was not assessed in enrolled patients. Consequently, no data on this specific issue are available for patients experiencing adverse new neurologic events or in-stent occlusion or restenosis.

Randomized studies are needed to confirm the early- and long-term durability of the CAS procedure using DLS.

## CONCLUSIONS

The 1-year results of the IRONGUARD 2 study suggest that the use of DLS could make it possible to achieve low rates of MACE and restenosis, regardless of patients' clinical and anatomical features or the procedural techniques adopted. Undeniably, our data should be validated in a randomized trial, prospectively evaluating results with a proper control population.

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## PERSPECTIVES

**WHAT IS KNOWN?** The need for increased plaque coverage to decrease the risk for debris dislodgement through stent struts has led to the design of DLS, which are able to trap and exclude thrombus and/or plaque debris to prevent embolic events from the target lesion. The safety and clinical efficacy of these devices have been proved up to 30 days. More recent studies have demonstrated that these devices are also associated with good clinical outcomes at 1-year follow-up, with a quite variable restenosis rate among the studies.

**WHAT IS NEW?** DLS could represent a solution in preventing events related to embolization through stent struts. The IRONGUARD 2 study represents the largest real-world study on patients undergoing CAS with DLS. The use of DLS has proved safe and effective in lowering periprocedural and postprocedural neurologic complications. Thirty-day and 12-month follow-up results confirm their role in effectively preventing brain embolic events. The restenosis rate with this particular type of stent is very low, with only 2 patients requiring reintervention.

**WHAT IS NEXT?** These data can be considered hypothesis generating toward the design of a large-scale clinical trial to definitively investigate the long-term safety and efficiency of this endovascular technique of carotid revascularization.

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