Independent Modular Filter for Embolic Protection in Carotid Stenting

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Background—Embolic protection during carotid artery stenting reduces the rate of thromboembolic events. The Wirion Embolic Protection System is used to deploy an independent distal filter using any 0.014″ guidewire. WISE study (Wirion Study Europe) evaluated the safety and performance of Wirion Embolic Protection System in patients undergoing carotid artery stenting.

Methods and Results—A prospective, multicenter, nonrandomized, open-label, single-arm study of carotid artery stenting in high surgical risk patients was performed. The primary end point, a composite of death, stroke, and myocardial infarction at 30 days, was compared with performance goal derived from historical controls. Secondary end points were components of the primary end point and the device, angiographic, procedural, and clinical success rates. Preplanned interim analysis was performed on the first 120 patients. At interim analysis, the primary end point was significantly lower for the Wirion Embolic Protection System group, compared with historical data (3.3% versus 6.3%, respectively; *P* value =0.0008). Analysis of primary end point components in the WISE group, compared with the historical control group, shows numerically lower mortality (0% versus 1.7%, respectively; *P*=0.21), stroke (2.5% versus 4.6%, respectively; *P*=0.18), and myocardial infarction (0.8% versus 1.5%, respectively; *P*=0.50). Device, angiographic, procedural, and clinical success was achieved in 99.2%, 99.1%, 98.3%, and 96.6% of cases, respectively.

Conclusions—The data suggest that independent modular filter use in carotid artery stenting in high surgical risk patients is safe and effective. The outcomes suggest that use of an independent modular filter may be associated with a lower rate of embolic complications associated with carotid stent placement.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01783639.

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Key Words: carotid artery ■ embolic protection ■ embolic stroke ■ myocardial infarction ■ stenting

The architecture of technologies for interventional cardiology evolved rapidly from the early fixed wire systems to the current guidewire-centered architecture and guidewire-compatible monorail device systems. The early transition to guidewire-centered architecture allowed to address complex vascular geometry and lesion morphology. The parallel development of a wide selection of guidewires with different specifications has supported the dramatic expansion of device-based cardiovascular therapy in the last 3 decades.

Distal embolic protection device (EPD) development in the stent-dominated cardiovascular interventions presented a unique challenge. Inherently, EPD must be deployed downstream from the target lesion. Thus, any catheter that will deliver the EPD distal to the treated lesion in a standard fashion (over the guidewire) will be trapped between the proximally deployed stent, at the lesion site, and the vessel wall. This dilemma led the EPD evolution toward 2 major directions: the fixed-wire distal protection systems and the proximal protection systems.[1–5]

The Wirion Embolic Protection System (EPS) was designed to deploy an independent modular distal filter for embolic protection, using any 0.014″ guidewire, at variable distance from the target lesion.

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WHAT IS KNOWN

- The presence of atherosclerotic disease in the internal carotid artery, its severity, and its symptomatic status yield an established annual risk of stroke.
- Therapy for patients with carotid atherosclerosis includes medical therapy aimed at reduction of embolism and control of the atherosclerotic progress. In selected patients, revascularization (carotid artery stenting [CAS] or carotid endarterectomy) should be considered.
- The main limitation of CAS is increased risk of procedure-related cerebrovascular events, as compared with that of carotid endarterectomy.
- Embolic protection devices significantly decrease the risk of periprocedural cerebrovascular events during CAS.

WHAT THE STUDY ADDS

- Improvement in embolic protection technology can optimize CAS outcome and potentially expand indications of CAS.

The objective of the WISE trial (Wirion Study Europe) was to evaluate the safety and performance of the Wirion EPS in the setting of carotid artery stenting (CAS).

Methods

Patients

The WISE trial was conducted in 10 medical centers in Europe from February 5, 2013, to January 23, 2014. The study was part of the requirements for regulatory submission of the Wirion for food and drug administration (FDA) clearance.

The enrolled patients had to be candidates for CAS, meet all the study's inclusion criteria (Table 1), fulfill at least 1 of the high surgical risk criteria for carotid endarterectomy (CEA; Table 1), and meet none of the exclusion criteria (Table 2). The protocol mandated significant carotid artery stenosis (measured by quantitative carotid angiography) using the NASCET (North American Symptomatic Carotid Endarterectomy Trial) methodology: ≥50% diameter stenosis for symptomatic patients and ≥80% diameter stenosis for asymptomatic patients. Because some of the inclusion and exclusion criteria were angiographic, a patient was enrolled in the study only after angiography was completed and a guidewire positioned distal to the target lesion. All patients signed informed consent forms before enrollment in the trial. The study included 4 clinical evaluations: baseline (pretreatment), postprocedure (0 to 4 hours post-procedure), predischarge (12 to 24 hours post-procedure), and end of follow-up (30±7 days post-procedure). Neurological evaluations, according to the National Institute of Health Stroke Scale, were performed by a neurologist or a National Institute of Health Stroke Scale–certified personnel blinded to the procedural details.

Study Design and Oversight

The WISE pivotal trial is a prospective, multicenter (n=10), nonrandomized, open-label, single-arm study enrolling high-risk surgical patients who are candidates for CAS, suitable for treatment with a single FDA-cleared carotid stent. The primary end point was a composite of major adverse cardiac and cerebrovascular events (MACCE) rate, including death, stroke, and myocardial infarction during the procedure and within 30 days, as determined by the Clinical Event Committee. The primary end point was compared with the published data of 4 US FDA-approved distal EPDs for CAS studies available at the time of the study design (n=1820; historical control; Table 3).[1–6] Secondary end points were the components of the primary end point and the various success rates (device, angiographic, procedure, clinical).

The trial protocol was designed by the Sponsor (Gardia Ltd.), with input from the investigators. The study was conducted in conformance with recognized Good Clinical Practice, International Conference on Harmonization guidance, and the principles laid out in the Declaration of Helsinki and relevant regulatory regulations. The study protocol and the informed consent were approved by the FDA under a 510K application by relevant national authorities in each country and by the local Institutional Ethics Committees at each participating center. An independent clinical research organization (Meditech, The Netherlands) managed monitoring and data collection. Clinical research forms were periodically monitored, and 100% source data verification was performed. Independent data management (Ganea, Belgium) ensured consistent and effective data management according to protocol. The Cardiovascular Research Foundation was responsible for statistical analysis, adverse clinical-event adjudication by the Clinical Event Committee, and monitoring of patient safety during the study by the Data Safety Monitoring Board, including an independent statistician. An independent central Angiographic Core Laboratory measured carotid artery reference diameter, minimal luminal diameter, NASCET percent diameter stenosis, and lesion length and analyzed lesion morphology, angiographic complications, and aortic arch morphology in all the procedures.

The Wirion EPS Design and Deployment

The Wirion EPS consists of an independent filter unit precrimped on the distal end of a rapid exchange delivery catheter, similar in form and function to a stent delivery catheter. The delivery catheter is compatible with any 0.014″ guidewire, 6- to 8-F guiding catheters and has a 1.1 mm crossing profile (Figure 1). The filter unit consists of a filter basket and a locking mechanism. The filter basket is made of a self-expanding metal (Nitinol) frame, compatible with a vessel diameter of 3.5 to 6.0 mm and a nylon filter mesh with 100 μm pores (n=≈1000/filter). The locking mechanism allows deployment of the independent filter unit on any 0.014″ guidewire at any location along the guidewire in the carotid artery. The locking mechanism is activated by the activating handle at the proximal end of the delivery catheter. The delivery system preparation requires only a 5 mL saline flush through the distal guidewire exit point.

The Wirion system's retrieval catheter is a rapid exchange catheter with a retractable nose cone, which allows smooth passage through the stented area, minimizing the risk of entanglement with the stent struts.

All investigators participating in the study were experienced operators in high-volume centers and were required to have training, including an in vitro training protocol with a dedicated simulator and 2 roll-in clinical cases, prior to enrolling patients for the study.

Prior to CAS, patients were pretreated with Aspirin 100 mg and Clopidogrel 75 mg daily for 3 days. Diagnostic angiography was performed according to the Angiographic Core Laboratory protocol. Then, the Wirion delivery catheter was prepped by flushing the distal tip with 5 mL heparinized saline. A 0.014″ guidewire was chosen at the discretion of the operator and positioned across the target lesion in a standard fashion. After the lesion was crossed with the 0.014″ guidewire, the delivery catheter was loaded on the guidewire and tracked to the desired location, and the filter unit was locked on the guidewire using the activating handle. Then, the delivery catheter was withdrawn while the filter unit was locked on the guidewire. As a result, the locked filter unit was unsheathed, and the filter's Nitinol frame expanded and opposed the vessel wall to optimized embolic capture (Figure 2). Stents were chosen, at the discretion of the operator, from a list of 4 FDA-approved carotid stents. CAS was performed according to the operator's discretion.

Table 1. Major Inclusion Criteria

1	Candidate for CAS, suitable for treatment with a single FDA-approved stent	
2	Vessel diameter 3.5–6.0 mm	
3	Landing zone ≥30 mm	
4	Significant carotid artery stenosis	
5	One of the following high surgical risk criteria:	
	Anatomic high-risk criteria:	Comorbid high-risk criteria:
	Recurrent stenosis after CEA	Unstable angina (CCS III/IV)
	Previous radical neck surgery or radiation therapy to the neck	CHF (NYHA III/IV)
	High cervical ICA lesions	LVEF<30%
	Contralateral occlusion	Requires major surgery, 31–60 days post-CAS
	Spinal immobility of the neck	Recent AMI (>72 h and <4 wk)
	Tracheostomy or tracheal stoma	Severe pulmonary disease (FEV1 of <30%)
	Any laryngeal nerve palsy and bilateral carotid artery stenosis	CAD in ≥2 unrevascularized vessels with stenosis ≥70%
		Age ≥75 y

AMI indicates acute myocardial infarction; CAD, coronary artery disease; CAS, carotid artery stenting; CCS, Canadian cardiovascular society angina class; CEA, carotid endarterectomy; CHF, congestive heart failure; FDA, food and drug administration; FEV1, forced expiratory volume at 1 s; ICA, internal carotid artery; LVEF, left ventricular ejection fraction; NASCET, North American Symptomatic Carotid Endarterectomy Trial; and NYHA, New York heart association congestive heart failure class.

Table 2. Major Exclusion Criteria

1	Total occlusion or near-occlusion (string sign) of the target vessel
2	Severe lesion calcification
3	Presence of an alternate source of emboli
4	Angiographically suspected thrombus
5	Significant ipsilateral proximal common carotid artery or distal (intracranial) lesion (≥51% diameter stenosis)
6	Evolving, acute, or recent stroke within the last 30 days
7	Major stroke with a residual neurological deficit
8	Patients with vertebrobasilar insufficiency symptoms only, without clearly identifiable symptoms referable to the targeted carotid artery
9	Major operation 30 days before or after the index procedure
10	Ipsilateral intracranial lesion that requires treatment
11	Preexisting stent in ipsilateral carotid artery or placement of a stent in contralateral carotid within 30 days of the index procedure
12	History of intracranial hemorrhage within 12 months
13	Condition that precludes proper angiographic assessment or prevents femoral arterial access
14	Uncontrolled hypertension
15	Contraindication to heparin, bivalirudin, aspirin, thienopyridines
16	Presence of a known sensitivity to radiographic contrast media, which cannot be controlled with premedication
17	History of bleeding diathesis or coagulopathy
18	Chronic renal insufficiency (serum creatinine >2.5 mg/dL)
19	Presence of carotid artery dissection or aortic arch anatomic anomalies
20	Dementia or a neurological illness
21	Patient is enrolled in another drug or device study protocol
22	Presence of severe pulmonary hypertension
23	Presence of intracranial pathology (eg, tumor, AVM, aneurysm)

AVM indicates arteriovenous malformation.

After stenting was completed, the retrieval catheter was used to recover the locked filter unit with the captured emboli. After CAS, patients were treated with Aspirin 100 mg daily and Clopidogrel 75 mg daily for 3 months.

Statistical Methods and Analysis

Continuous variables were presented as means with standard deviations. Dichotomous variables were presented as frequencies, in percentages.

The study was designed to test the primary null hypothesis that the primary end point in carotid stenting using the Wirion EPS is equal to or higher than the performance goal derived from historical controls. An adjustment of the weighted average of 30-day expected MACCE of 6.3% (Table 3) derived from the control studies was calculated to specify that the highest composite 30-day MACCE rate is still within an acceptable range of the outcomes of the published studies. A margin of 5.7% above the weighted average of MACCE rate was selected to establish a performance goal. That is, the upper boundary of the 95% confidence interval around an observed 30-day composite MACCE would be less than a performance goal of 12%. The primary analysis data set included all enrolled patients in the study. Thus, technical failures were included in the primary analysis.

For planning purposes, it was assumed that the number of subjects with MACCE (primary end point) would meet the assumptions for the normal approximation to the test of a single hypothesized population proportion. Specifically, it was assumed that the proportion of subjects who meet the primary end point would exceed 5%. In the event that this assumption for the normal approximation is not met, the probabilities would be calculated using the exact binomial expansion.

Components of the primary end point (death, stroke, and myocardial infarction) were analyzed. A sample size of n=240 was calculated for 80% power and 7% loss of follow-up.

A preplanned interim analysis by the Data Safety Monitoring Board was performed on the first 120 patients after the 30-day follow-up visit. A 0.0015 alpha criteria, based on O'Brien Fleming boundaries, corresponding to 2-sided 99.7% confidence interval was set for the interim analysis.

For poolability analysis, we ran a 2-sided generalized Fisher exact test to assess the homogeneity of the failure rates across the active sites of the WISE study.

The data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Patients (n=120) were enrolled between February 5, 2013, and January 23, 2014. Twenty roll-in cases (2 per site) were performed with no MACCE.

Table 3. Historical Control Data

Study	EPD System	N	30-Day MACCE
ARCHeR 2[1]	Accunet	278	8.6%
ARCHeR 3[1]	Accunet	145	8.3%
BEACH[4]	FilterWire	480	5.4%
MAVERiC 1 and MAVERiC 2[2]	GuardWire	498	5.4%
CREATE[5]	Spider	419	6.2%
		∑=1820	Weighted average=6.3%

ARCHeR indicates Acculink for Revascularization of Carotids in High Risk Patients trial; BEACH, Boston Scientific Embolic Protection, Inc (EPI): A Carotid Stenting Trial for High-Risk Surgical Patients; CREATE, Carotid Revascularization With ev3 Arterial Technology Evolution; EPD, embolic protection device; MACCE, major adverse cardiac and cerebrovascular events; and MAVERiC, Medtronic AVE Self-Expanding Carotid Stent System With Distal Protection in the Treatment of Carotid Stenosis.

Consecutive patients (n=142) were screened for the WISE study; screen failures (n=22) were because of insignificant carotid narrowing at the baseline carotid angiography or absence of criteria for high surgical risk. As per study protocol, the preplanned interim analysis was performed when 120 patients were recruited and had completed the study follow-up. Out of the 120 patients, in 1 patient, the Wirion system failed to deliver the filter because of torturous vasculature, and the patient underwent CAS using a proximal EPS. Results from all 120 patients were analyzed.

The demographic characteristics of the WISE study population, at the interim analysis, as compared with those of the historical controls (Table 4), suggest older (74.9 versus 72.0 years, respectively; *P*=<0.01) male (male sex 72.5% versus 62.9%, respectively; *P*=0.03) population with similar prevalence of comorbidities, including hypertension (88.3%. versus 88.0%, respectively; *P*=0.91), diabetes mellitus (34.2% versus 34.0%, respectively; *P*=0.97), and heart failure (18.3% versus 19.1%, respectively; *P*=0.83). More patients in our study, compared with those in the historical controls, were asymptomatic (88.3% versus 73%, respectively; *P*<0.01) and with lower rates of history of stroke (10.8% versus 25.5%, respectively; *P*<0.01) and recent TIA (5% versus 28.3%, respectively; *P*<0.01).

Angiographic and intervention data at the interim analysis revealed that CAS involved the right and left carotid arteries in similar proportions (46.7% and 53.3%, respectively). The lesions were mostly (87.5%) de novo lesions with significant narrowing (quantitative carotid angiography measurements: 84.2±7.8 NASCET percent diameter stenosis) and with substantial proportions of high-risk morphology, including significant calcifications (32.5%) and ulceration (19.2%; Table 5).

At the interim analysis, 4 (3.3%) patients had MACCE. The primary end point of the WISE study group was significantly lower than that of the historical data (3.3% versus 6.3%, respectively; *P*=0.0008; Figure 3). The Clopper–Pearson Confidence boundary for 4 events was 11.38%, lower than the predefined 12% performance goal. The null hypothesis

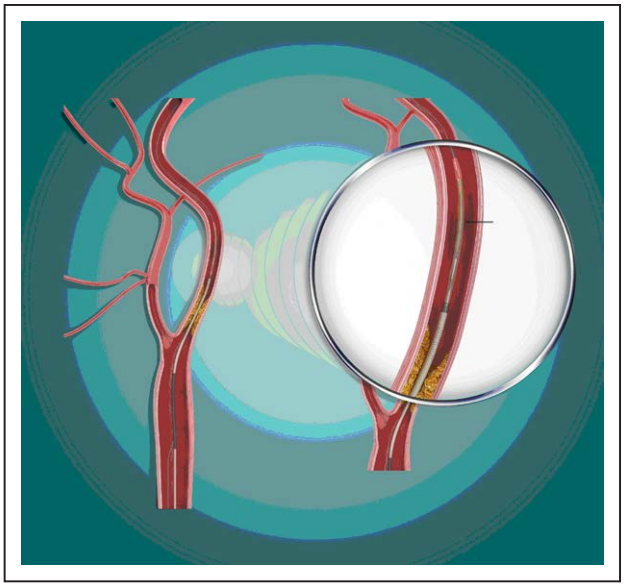

Figure 1. The Wirion EPS delivery catheter, loaded on a 0.014″ guidewire, across an atherosclerotic lesion in the internal carotid artery. The Wirion EPS delivery catheter consists of an independent precrimped filter unit (arrow) at the distal end of a rapid exchange delivery catheter. The delivery catheter is compatible with any 0.014″ guidewire. EPS indicates embolic protection system.

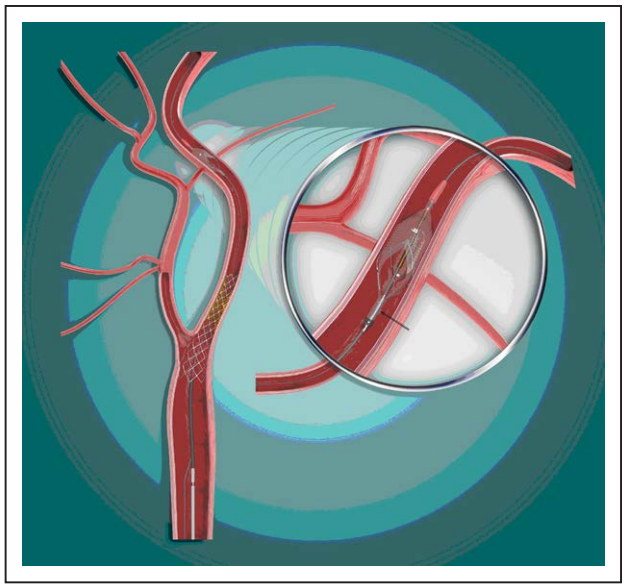

Figure 2. The independent filter unit deployed on a 0.014″ guidewire after carotid artery stenting. The filter unit consists of a self-expanding Nitinol frame with a nylon filter mesh and a locking mechanism. The locking mechanism (arrow) allows deployment of the independent filter unit on any 0.014″ guidewire at any location along the vessel.

Table 4. Patients' Demographic Data

Demographics	n=120
Age, y	74.9±8.0
Male sex	72.5%
BMI	26.5±3.9
Smokers	47.5%
Diabetes mellitus	34.2%
Hyperlipidemia	79.2%
Hypertension	88.3%
PAD	36.7%
Recent TIA	5.0%
History of stroke	10.8%
CHF	18.3%
History of CAD	43.3%
Previous CABG	8.3%
Previous AMI	14.2%
Previous PCI	27.5%
ACS	4.2%
Valvular heart disease	8.3%
Recent or recurrent arrhythmia	12.5%
Previous carotid procedures	25.8%
Current carotid disease	
Symptomatic	11.7%
Asymptomatic	88.3%

ACS indicates acute coronary symptom; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

Table 5. Carotid Artery Stenting Data

Carotid Artery Stenting Data	n=120
Procedure duration, min	55.9±25.9
Type III aortic arch*	7.5%
Target lesion location	
Right carotid artery	46.7%
Left carotid artery	53.3%
Lesion site	
Internal carotid artery	83.3%
Bifurcation	15.0%
Other	1.7%
Lesion type	
De novo	87.5%
Restenosis	12.5%
Lesion length, mm*	13.5±6.6
Reference diameter, mm*	4.4±0.8
Minimal luminal diameter, mm*	1.75±0.71
Preprocedure stenosis* (NASCET % diameter)	61.2±15.1
Lesion morphology*	
Calcification	
None	21.7%
Mild	45.8%
Moderate	25.8%
Severe	6.7%
Ulcerated lesion	19.2%
Visual thrombus	0%
Contralateral disease	36.7%
Stent technical details	
Stent diameter, mm	7.5±1.2
Stent length, mm	32.7±6.65
Stent type	
Acculink	1.7%
Precise	42.5%
Wallstent	24.2%
Xact	30.8%
Other	2.5%
Postprocedure % stenosis*	7.3±8.3%

NASCET indicates North American Symptomatic Carotid Endarterectomy Trial.
*Core laboratory data.

was, therefore, rejected based on an α=0.0015. Thus, at the interim analysis, the study met the predefined success criteria and was terminated at the recommendation of the Data Safety Monitoring Board. Five MACCE events occurred in 4 patients, of which 3 events were adjudicated as procedure related. Two events were adjudicated by the Clinical Event Committee as neither device related nor procedure related (Table in the Data Supplement).

No significant differences between proportions of MACCE in the various sites were detected.

Components of the primary end point in the WISE group, as compared with those in the historical control group, shows numerically lower mortality (0% versus 1.7%, respectively; *P*=0.21), stroke (2.5% versus 4.6%, respectively; *P*=0.18), and myocardial infarction (0.8% versus 1.5%, respectively; *P*=0.50; Figure 4). Thus, the combined end point of 30-day death and stroke rates was 2.5%.

Device success was achieved in 99.1% of cases (119/120). In 1 case, after the insertion of the delivery catheter into the guiding catheter, the case was aborted because of a tortuous vascular anatomy. Angiographic success was achieved in 99.1% of cases (119/120). One patient had postprocedure transient flow impairment. Hence, procedural success was achieved in 98.3% of cases (118/120). Clinical success was achieved in 96.6% of cases (116/120) as a result of 2 MACCE adjudicated as device related or procedure related.

Average procedure duration was under 1 hour (55.9±25.9 minutes), with fluoroscopy time of 13.6±10.5 minute. Time from femoral sheath insertion to filter deployment was 7.5±7.2

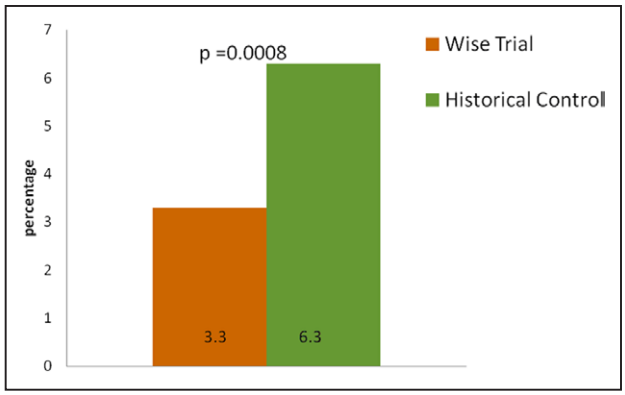

Figure 3. Primary end point of the WISE trial (Wirion Study Europe) vs historical control data. Primary end point was a composite of major adverse cardiac and cerebrovascular events rate (death, stroke, myocardial infarction) during the procedure and within 30 days of follow-up.

minutes. The investigators chose to use 10 different types of guidewire produced by 5 different manufacturers. Standard work-horse-type guidewire was chosen in 63.7% of the cases, and extra support/stiff-type guidewires were chosen in 35.4% of the cases. Of the guidewires used, 9.6% had hydrophilic coating. There was no need for balloon predilatation prior to filter deployment.

Stents were chosen at the discretion of the operator: Acculink in 1.7% of the patients, Precise in 42.5%, Wallstent in 24.2%, Xact in 30.8%, and others in 2.5% of the CAS patients.

Discussion

Carotid atherosclerosis accounts for ≈10% of ischemic strokes. The presence of atherosclerotic disease in the internal carotid artery, its severity, and its symptomatic status yield an established annual risk of stroke—patients with asymptomatic stenosis (60%–99%) have an annual 2% to 2.5% risk of stroke. Symptomatic carotid stenosis (>70%) carries a 10% to 15% annual risk of stroke.[6–9] Current therapy of patients with carotid atherosclerosis includes medical therapy aimed at reduction of embolism and control of the atherosclerotic progress. In selected patients, revascularization (CAS or CEA) should be considered.

Currently, CAS is an accepted alternative to CEA for the treatment of patients with increased risk of complications associated with surgery.[10,11] The CREST trial (Carotid Revascularization Endarterectomy Versus Stenting Trial), the largest randomized trial to date, recently suggested equipoise for CAS and CEA even in patients with average risk of CEA complications.[12]

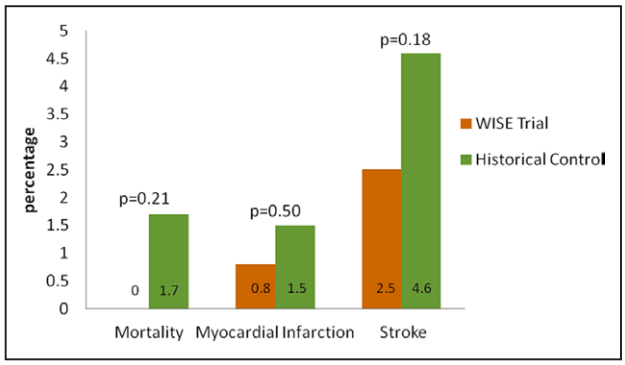

Figure 4. Secondary end points of the WISE trial (Wirion Study Europe) vs historical control data.

The main limitation of CAS is increased risk of thromboembolic-related cerebrovascular events, as compared with that of CEA.[12] The majority of embolic events (≈90%) is directly related to the CAS-generated emboli in the territory of the treated vessel, which can potentially be prevented by optimal embolic protection technology.[13] Meta-analyses and reviews of the use of EPD in CAS[14–16] suggest that EPDs significantly decrease the risk of periprocedural thromboembolic events during CAS.

The limited compatibility of contemporary EPS with the array of 0.014″ guidewires may be reflected in the limitations of present CAS: (1) an extended operator's learning curve[17–19]; (2) device-specific learning curve. Each EPD requires an individual learning curve; and (3) relationship between thromboembolic events and complex vascular geometries and high-risk lesion morphological features.[20,21]

The Wirion EPS design, including full guidewire compatibility, has a potential for ease of use, excellent deliverability, short learning curve, and rapid and safe crossing of the target lesion, with limited considerations for vessel tortuosity and lesion morphology.

In the WISE study, at the interim analysis, the study met the predefined success criteria and was terminated at the recommendation of the Data Safety Monitoring Board. The 30-day MACCE was significantly lower for the Wirion group, as compared with the historical controls. Analysis of components of the primary end point in the WISE group show numerically lower mortality, stroke, and myocardial infarction when the Wirion EPS is used for embolic protection during CAS, as compared with that of the historical control group. In the WISE study, the investigators chose 10 different types of guidewires to optimize results. Thus, the data suggest that the unique features of a guidewire-centered delivery system coupled with an independent modular filter may translate into clinical benefit and ease of use in CAS.

CAS outcomes have improved over time. Data published later than the historical control publications showed lower rates of adverse events in CAS. The CAPTURE 2 registry (Second Phase of Carotid RX Acculink/RX Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events)[22] reported a 30-day MACCE rate of 3.5%. Recently published studies suggest further improvement in CAS. Rosenfield et al[23] and Matsumura et al,[24] using a new guidewire-centered distal EPD, reported a 30-day MACCE rate of 2.9% and 2.3%, respectively. These data, combined with the WISE trial data, suggest that improvement in outcome could be related to improved embolic protection technology and significant advances in cognitive and technical expertise that have developed since the historical control studies were conducted.

Study Limitations

The experimental design of the WISE trial compares 30-day outcomes of CAS with the Wirion EPS to a weighted

composite of historical data obtained from trials of 4 different distal EPDs. The objective performance criteria used in the study were derived from the published data of these 4 US FDA-approved distal EPD trials available at the time the present study was designed.

Raw data were not available for analysis. The available data included rates of MACCE and only limited demographic and baseline data. Of note, in the WISE trial, a healthier population (lower rates of symptomatic patients, prior stroke, and recent TIA) was treated using, in the majority of the cases (74.9%), stents not used in the historical control trials (Table 5), a fact that may account in part for the improved outcome in this trial.

Sources of Funding

This work was supported by Gardia Medical Ltd, manufacturer of the Wirion EPS and sponsor of the WISE trial.

Disclosures

Dr Rosenschein is the founder of Gardia Medical Ltd, manufacturer of the Wirion EPS and sponsor of the WISE trial. The other authors report no conflicts.

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Supplemental Table. MACCE Patients' Data

MACCE patients	Description	CEC Adjudication
Pt 1 2 minor strokes	Post procedure dysarthria lasting 48hrs (bilateral new MRI lesions)	Procedure related Probably device related
	Ipsi-lateralight retinal artery emboli @ day 7	Procedure related Not device related
Pt 2 Minor stroke	Post procedure dysarthria (NIHSS 2 @ discharge; NIHSS 1@ 30 day f-u)	Procedure related Device related
Pt 3 Major stroke	Contralateral ischemic stroke following new onset of A Fib @ day 7	Not procedure related Not device related
Pt 4 NSTEMI	Chest pain and biomarker rise @ day 14. Angiography- LMCA and 3VD. Underwent CABG	Not procedure related Not device related