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A permanent common carotid filter for stroke prevention in atrial fibrillation: *Ex vivo* and *in vivo* pre-clinical testing

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ABSTRACT

Background and purpose: A novel, permanent, bilateral, common carotid artery (CCA) coil filter implant was designed to capture stroke-producing emboli in atrial fibrillation patients. Under ultrasound guidance, it is automatically deployed through a 24-guage needle and is retrievable up to 4 h post-procedure. We assessed the feasibility, safety, and effectiveness of the CCA filter in pre-clinical testing.

Methods: In a pulsatile flow simulator, the filter's embolic capture efficiency and integrity of simulated (1.2 mm diameter nylon balls) and actual thromboemboli were tested. Implant insertion, retrieval, and chronic safety were tested in sheep by ultrasound and X-ray. At termination, the CCAs were explanted and examined by pathology, histopathology and scanning electron microscopy. The fate of captured emboli was evaluated in sheep 3 weeks after upstream injection of autologous thromboemboli.

Results: In the flow simulator, 10 filters captured 29 of 29 (100%) 1.2 mm diameter nylon balls. In the thromboemboli integrity test, all captured thromboemboli (99 of 99) were adherent to the filter, without fragmentation. All sheep (n = 30/60 implants) underwent successful CCA filter implantation. During follow-ups at 4, 12, 13, 23, and 31 weeks (6 sheep/12 implants at each follow-up), there were no (0%) major bleeds, CCA damage/stenosis, implant migration, flow obstruction, or thrombi detected by ultrasound. Two organized microthrombi (<100 μm) were observed by histopathology at the puncture site. After 3 weeks, autologous captured thromboemboli (n = 10) either completely regressed (5 of 5) or did not progress (5 of 5).

Conclusion: These favorable pre-clinical results prompt clinical testing of the CCA filter in stroke prevention clinical trials.

1. Introduction

A novel, permanent, bilateral, common carotid artery (CCA) filter has been developed to capture clinically-significant emboli >1.5 mm in size from reaching the cerebral anterior circulation and causing stroke. It is designed to be easily placed through a single transcutaneous puncture (24G) from directly atop the carotid artery at the neck, and is intended for use in atrial fibrillation (AF) patients at high risk for stroke who may or may not be treated with OAC. We recently reported the results of the first-in-human clinical trial of this CCA filter, *CAPTURE*, in a series of AF patients with contraindications to oral anticoagulants [1]. In ongoing safety study (*CAPTURE 2*), and consecutive pivotal randomized control trial, the CCA filter is intended for use in AF patients who are treated with OAC and remain at high risk for stroke (*i.e.* post recent stroke). Herein, we report on the pre-clinical testing of this CCA filter, including *in vitro* flow simulators and an *in vivo ovine* model.

2. Material and methods

2.1. The CCA filter

The CCA filter (Vine™; Javelin Medical Ltd., Israel) is made from a super-elastic nitinol wire with a circular cross-section (diameter 240 μm). In the un-deployed state, the implant assumes a substantially linear shape within the lumen of a 24-gauge insertion needle. In the deployed state, the implant comprises a helix that resides within the CCA lumen, a linear stem that traverses the CCA wall and two anchors (internal and external) (Fig. 1). The helix includes 3 segments: supporting coils, filtering portion, and leading coils. The filtering portion is a cone

Abbreviations: AF, atrial fibrillation; CCA, common carotid artery; OAC, oral anticoagulation; NOAC, non-warfarin oral anticoagulation; SEM, scanning electron microscopy; TIA, transient ischemic attack.

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with an apex facing upstream, the distance between consecutive coils is approximately 1.0 mm. The filter is inserted using the CCA inserter under ultrasound guidance; the insertion needle punctures the neck skin and the CCA wall, and the implant is automatically deployed upon activation of the CCA inserter operating button (Online Movie 1). Notifications and alarms (audio - beep and visual – led) are built into the inserter. The implant can be retrieved up to 4 h following implantation using a pulling wire that is connected to the stem and extends outside the patient's skin. After cutting the pulling wire, the implant can still be extracted by an open carotid surgery ("endarterectomy like"). The implant is available in 10 sizes (0.5 mm increments) to accommodate CCA diameters between 5 mm and 10 mm. CCA carotid sizing is quantified by ultrasound measurement of intraluminal diameter (endothelium to endothelium), relative to which the CCA Filter is oversized 0.2 mm–0.7 mm.

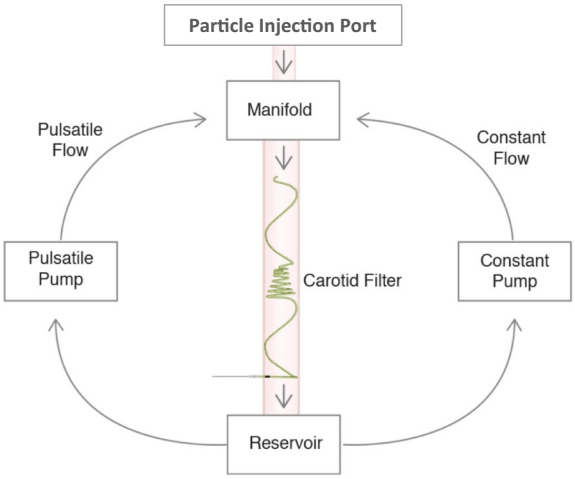

Fig. 2. Flow simulator schematic diagram.

2.2. In vitro embolic capture efficiency: pulsatile pump bench-top model

The CCA filter's embolic capture efficiency was evaluated in a pulsatile flow simulator (Fig. 2) that simulates human carotid arterial blood flow. This *in vitro* bench top model is an accepted method to evaluate the performance of filtering devices [2]. The CCA flow simulator includes pulsatile and constant flow pumps that circulate a glycerol solution (37%) in a silicone tube manifold at varying flow rates, representative of the human CCA diameter and flow, respectively [3]. The simulated flow parameters were determined by ultrasound pulse wave as follows: basal velocity – 20 ± 5 cm/s, peak systolic velocity – 120 ± 10 cm/s, and beats per minutes – 70–80.

2.3. In vitro capture efficiency evaluation

Nylon balls (n = 29) simulating emboli with a diameter of 1.2mm were individually released into the flow for each tested implant (sizes 5.0 mm–10 mm, 0.5mm jumps).

2.4. In vitro integrity of captured thrombo-emboli

Ovine blood was drawn and placed in silicone tubes of 3.0 mm diameter. After 2 days, the tubes were cut at the desired thrombus length,

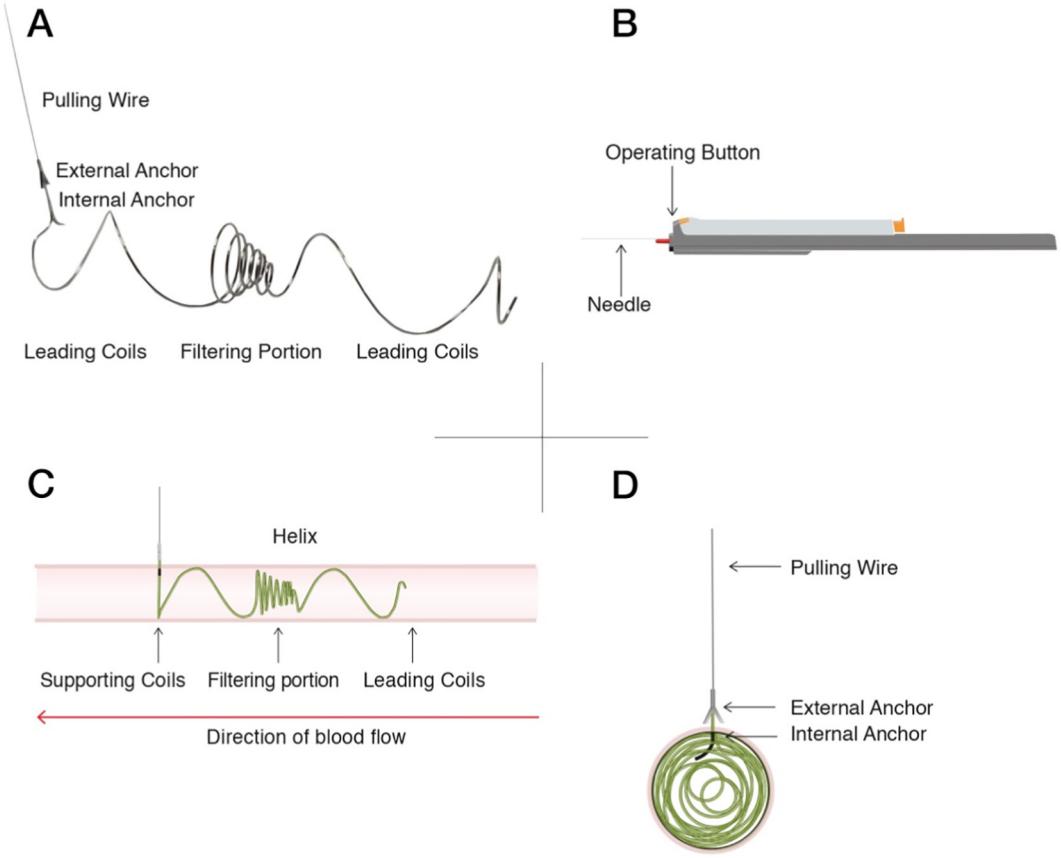

Fig. 1. A: The CCA Filter. B: The CCA Filter inserter. C & D: the deployed CCA Filter, side (C) and front (D) views.

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and thrombi were extracted. The thrombi were injected into the flow and their integrity after capture was monitored visually in real time.

2.5. Sheep as an animal model

Sheep (Ovis Ares) were selected as the animal model because the *ovine* CCA is superficial, visible under ultrasound, and displays a range of diameters and peak blood flow velocities representative of human CCA diameters and peak flows [4–5]. The sheep coagulation system is considered a severe test of implant thrombogenicity [6–8] demonstrating rapid initiation of contact activation pathways, significantly shorter collagen induced thrombus formation time (CITF) [23], high levels of Factor VIII and Factor XII, and low Protein C [8] indicating hypercoagulability of *ovine* blood relative to humans. Greater overall clot firmness and a reduced capacity for clot lysis have also been documented in sheep [8]. Moreover, *ovine* platelets are not responsive to aspirin and only ~25% are responsive to clopidogrel [9–10].

2.6. Study sites, animal grouping, and follow-up

The study was conducted in 2 GLP-compliant sites, NAMSA France and Asaf Harofe Israel, and approved by the local animal ethics committees. The study included 5 groups of 6 sheep; follow ups were performed at 4, 12, and 31 weeks (France), and 13 and 23 weeks (Israel) after implantation.

2.7. Study design

Sheep were selected based on their CCA diameter. General anesthesia was obtained by premedication of intramuscular ketamin 10 mg/kg and xylazine 0.2 mg/kg and maintained by inhalation of O_2-isoflurane 2%.

For each sheep, an implantation was attempted under ultrasound imaging guidance into each CCA (30 sheep, 60 implants). Implants were oversized 0.2–0.7 mm relative to the maximal (systolic) CCA diameter at the implantation site. Following implantation, the pulling wire was cut close to the skin, and the stub was tucked under the skin. After implantation, the animal stayed in a farm under standard husbandry conditions. The antithrombotic regimen included: i) clopidogrel starting 5 days pre-procedure until termination (75 mg/day), ii) intravenous heparin during the procedure (100 U/kg + maintenance dose to achieve a target ACT > 250), and iii) enoxaparin 2 days post-procedure (80 mg × 2/day).

The acute performance and handling characteristics of the CCA inserter was evaluated following implantation (needle visualization, CCA puncture, implant deployment, and needle withdrawal). Procedural and chromic safety endpoints (major bleeding, thrombus on implant, CCA damage or occlusion, proper position of implant) (see Supplement) were determined by ultrasound and X-ray examination during the procedure and at follow-ups. At termination, each CCA was isolated by careful dissection of the surrounding soft tissues, and anatomic abnormalities were recorded. The CCA was then harvested and fixed in formalin. After fixation, samples were examined by microscopy and histopathology (n = 10 sites per time-period) and scanning electron microscopy (SEM) analysis (n = 2 sites per time period). SEM analysis included searching for cell adhesion, thrombus deposits, and the extent of endothelial layer developed over the implants. One undeployed implant served as a reference for structural characterization.

2.8. CCA filter retraction – ovine safety study

In 3 sheep, 2 implants were deployed in each CCA (n = 12). Six additional punctures (one in each CCA without implant deployment) were performed without implant deployment (positive controls). At 4 ± 0.5 h following deployment, all implants were retracted under ultrasound guidance. At day 12 post-procedure, implantation sites were evaluated by ultrasound and then harvested for histopathologic evaluation.

2.9. Fate of emboli study in sheep

Ten implants were deployed bilaterally in 5 sheep. Four weeks after implantation, autologous thrombo-emboli 2–5mm in size were injected *via* a femoral guiding catheter directly into the carotid artery - one embolus per implant. Capture was confirmed by B mode ultrasound. An ultrasound examination was performed at 7 ± 1 days after emboli were captured. At the end of the study (3 weeks after thrombo-emboli capture), implants were examined by ultrasound and X-ray and harvested for histopathologic evaluation.

3. Results

3.1. In vitro capture efficiency and integrity of captured thrombo-emboli

In the flow simulator, each of 10 tested implants (sizes 5 mm–10 mm), captured 29/29 (100%) of the nylon balls. In the *ovine* thrombo-emboli integrity study, all (99/99) captured thrombo-emboli were firmly adhered to the CCA filter, and no (0%) embolus breakdown was observed.

3.2. Chronic ovine safety study

Overall, 30 of 30 animals (100%) survived and were in good health until sacrifice at the termination of the study. A total of 66 implantation attempts were performed to successfully deploy 60 implants (91% implantation success rate; also see Online Movie 2). In 4 cases, the implant was improperly positioned, and was therefore retracted and successfully replaced. In 1 case, there was a CCA puncturing failure due to a damaged needle tip. In 1 case, the implant was stuck in the needle, at which point the CCA inserter performed an immediate shutdown and alarmed the operator (audio – beep and visual - red led blinking) so that a new CCA inserter was utilized.

3.3. Procedural and implant safety

In all 60 implants at all subsequent follow-ups (4, 12, 13, 23, and 31 weeks), ultrasound and X-ray evaluations revealed no (0%) events of bleeding, thrombus on filter, CCA damage or occlusion, or improper implant position (Table 1). Representative images of the CCA filter on ultrasound and X-ray are shown in Fig. 3.

3.4. Pathological analyses

There were no macroscopic pathological abnormalities observed at the implantation sites and surrounding tissues. The histopathologic analysis revealed the implants to be properly deployed, stable, and secured at the implantation sites in all specimens harvested at 4, 12, 13, 23, and 31 weeks (10 in each time period). In 2 cases (week 4 and week 31 groups) a small white organized thrombus (50 μ–100 μ) was observed at the puncturing site firmly adhered to the internal anchor. In all implants at all follow-ups, neointimal growth (NIG) was minimal and, if any, observed at a few contact points of the filter wire with the CCA wall. The main histopathology findings are shown in Table 2. There were no differences in histopathology findings between samples at 4, 12, and 31 weeks (NAMSA France Study, n = 10 per time period). Representative histopathology images are shown in Fig. 4 and Fig. 5. The observed distant organs (lungs, liver, kidneys, spleen, heart and brain) showed no macroscopic signs of thrombosis, infarct, or inflammation. There were no microscopic signs of thrombosis in the brain or evidence of embolization in the smaller vessels in the brain in any animal.

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Table 1
Chronic phase endpoints in ovine studies (x-ray and ultrasound).

	Study group				
	4 Weeks N = 12	12 Weeks N = 12	13 Weeks N = 12	23 Weeks N = 12	31 Weeks N = 12
CCA damage or occlusion	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)
Major bleeding	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)
Thrombus on filter	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)
Proper implant position	12/12 (100%)	12/12 (100%)	12/12 (100%)	12/12 (100%)	12/12 (100%)

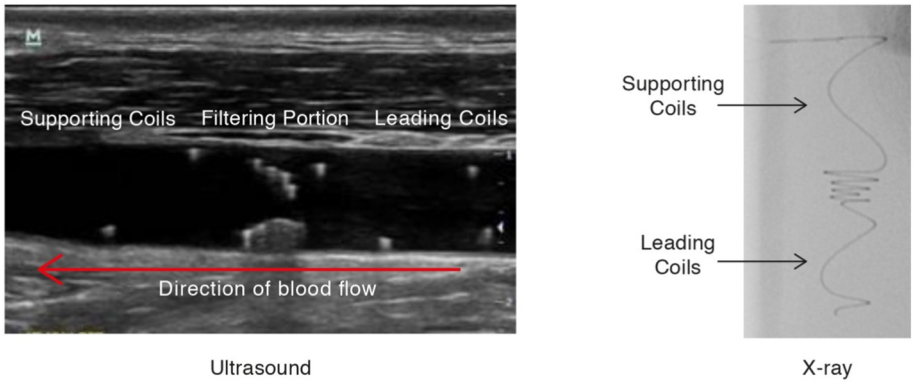

Fig. 3. Ultrasound (A) and X-Ray (B) images of the deployed filter.

Table 2
Histopathology findings.

	Findings (N = 30) (NAMSA France, weeks 4, 12, and 31)
Anchors/stem	• Remolded fibrotic tissue around anchors stem • Healed perforated *endo*-luminal side • Mural organized thrombus (50 μ - 100 μ) (2 cases)
Supporting coils	• Trans medial penetration (7 cases) • No remarkable neointimal growth • No thrombus
Filter	• No remarkable neointimal growth • Slight endothelial coverage (3 cases) • No thrombus
Leading coils	• No vascular wall compression • No remarkable neointimal growth • No thrombus

3.5. Scanning electron microscopy analysis

The SEM analysis of all groups (2 of 10 in each time period) showed a properly deployed and secured implant with only minimal signs of fibrin and blood cell deposits. No evidence of thrombus deposit was noted at the implant surface. Minimal NIG was seen at the anchors near the puncture sites and at a few contact point of the wire with the CCA wall. Representative SEM images are shown Fig. 6

3.6. CCA filter retraction safety in sheep

Ultrasound examinations showed no major bleeding or CCA damage in 12 of 12 insertion sites and 6 of 6 control sites at 4 ± 0.5 h post-implantation and at 12 days post-recovery. Minor hematomas were observed during macroscopic examination of surrounding tissues at 3 implanted sites and 3 control sites. Histopathology findings of the CCA wall and surrounding tissue were minimal and observed in both retraction and control sites.

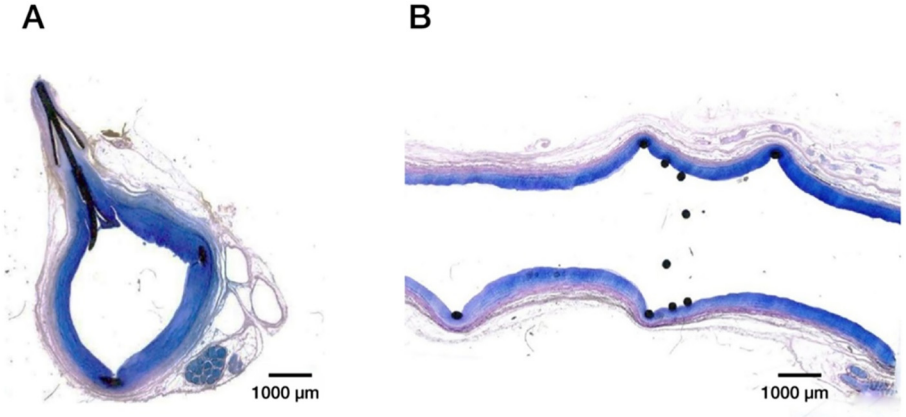

Fig. 4. Histopathology of the carotid artery with the CCA filter *in situ*. A: transverse section at the plane of the anchors. B: longitudinal section at the filter.

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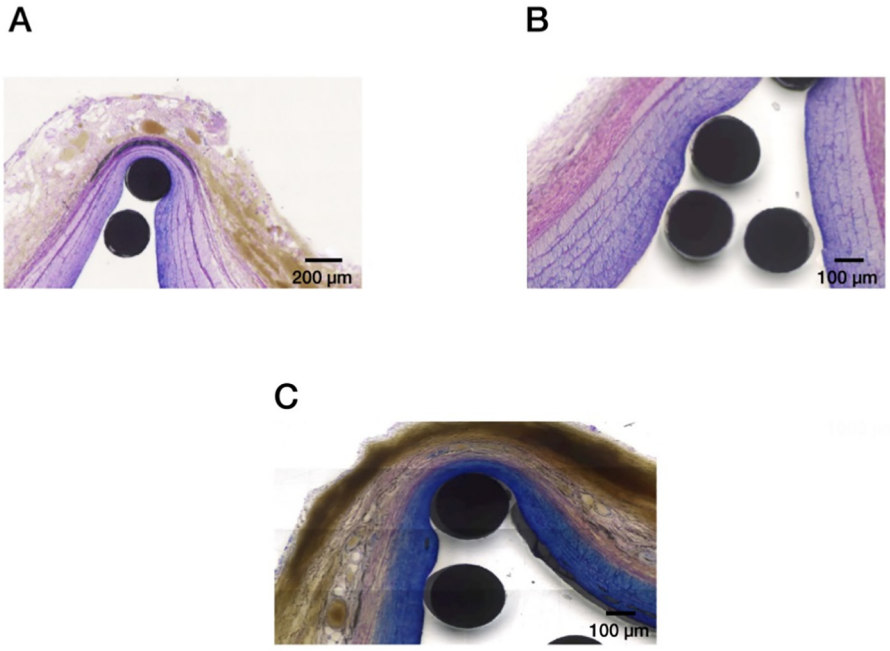

Fig. 5. Histopathology of the carotid artery with the CCA filter *in situ*. A: 4 weeks. B: 12 weeks. C: 31 weeks.

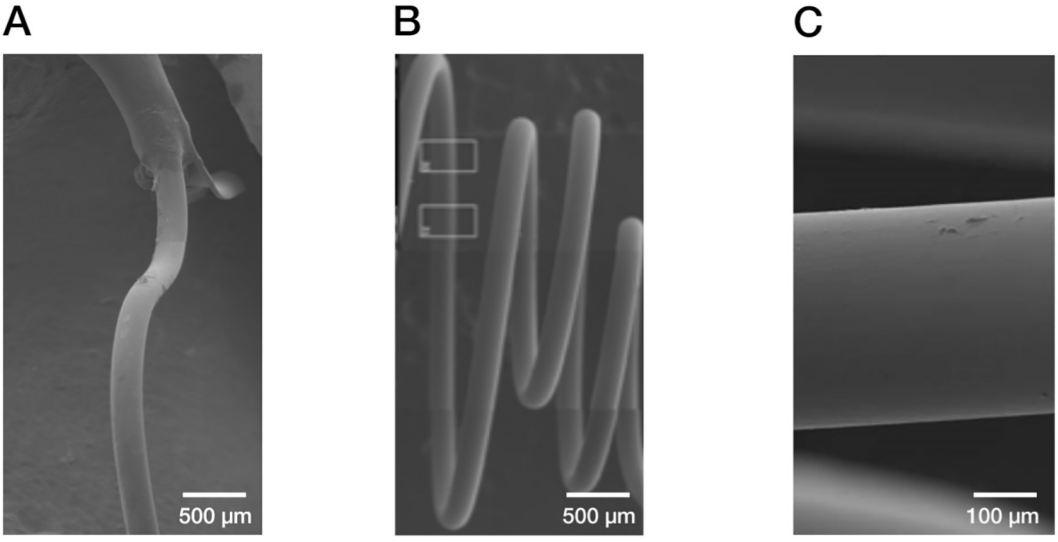

Fig. 6. Scanning Electron Microscopy imaging of the chronically-implanted CCA filter. A: internal anchor X40. B: filter X40. C: filter wire X200.

3.7. Fate of captured emboli in sheep

In vivo embolic capture was confirmed by B-mode ultrasound at 9 of 10 implants. At 3 weeks post embolic capture, 5 thrombi were observed on 5 harvested implants. All observed thrombi adhered to the filtering portion of the implant. The sizes (largest dimension) of the emboli were 2 mm–5 mm, approximately the same size at release. There was no discoloration or any signs of thrombosis in the vessel lumen in any of the samples. In all cases, no obstruction of blood flow was observed

4. Discussion

In this study, we performed *in vitro* flow simulation and pre-clinical *in vivo* assessment of a novel carotid coil filter to capture simulated and actual thromboemboli exceeding 1.2 mm in size. Together, these experiments demonstrated that the filter can capture these thromboemboli, and that the thromboemboli don't fragment upon capture.

The technical ovine deployment of the CCA filter went well in our experience. This supports the feasibility of limited procedural risk with deployment in the human CCA, as we have confirmed and reported in the first human experience [1]. The low procedural risk observed is consistent with evidence that inadvertent carotid artery puncture during jugular cannulation is innocent, despite its relatively common occurrence – happening in ~3% of cannulations [11]. It is also consistent with data showing that CCA punctures with needles smaller than 18G are innocent [12–13]. Bleeding from the puncture site can be easily stopped by applying local pressure for just several minutes. The risk of inadvertent plaque rupture during carotid puncture is mitigated by excluding atheromatous CCA segments by pre-procedure ultrasound screening.

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There was no thrombus identified on the implant wire despite the minimal neointimal growth and continuous contact of blood with the bare metal wire and despite the poor response of sheep to antiplatelet drugs. This observation is in line with the low rate (<1%) of thrombus formation on "free floating" stent and graft struts crossing coronary [14–15], renal [16–18], and carotid [19–20] ostia.

In histopathology and SEM, neointimal growth was not seen on the filtering portion and was minimal on the supporting and leading coils that are in contact with the carotid arterial wall. This observation is likely related to the relatively low radial force exerted by the implant on the arterial wall (5%–10% oversized relative to CCA systolic diameter) as compared to arterial stents [21]. For example, a standard 8 mm stent spanning the carotid bifurcation from a 6 mm common carotid artery to a 4 mm internal carotid artery results in ~30% and 100% oversizing, respectively. The CCA filter is fixed in place by a stem traversing the arterial wall and equipped with an extra- and intra-luminal anchor. Accordingly, migration is completely eliminated, irrespective of the relatively low friction between the implant and the arterial wall.

Distal embolization of thrombi that potentially formed on the implant (potentially resulting in cerebral infarcts) could not be ruled out in sheep because the distal carotid artery in sheep, as in the vast majority of quadrupeds, ramifies into a net of micro-arteries (Rete Mirabilis) [22] that would capture all proximately originating emboli. However, pre-clinical and clinical experience in other vascular settings suggest that distal embolization of thrombotic material dislodged from stent struts is most probably a rare event; kidney infarcts were not observed in cases of renal ostia crossed by aortic stents in swine [17] and humans [18]. The potential risk of distal embolization from the implant is therefore likely low.

The fate of captured thrombo-emboli was tested in a human-carotid-flow simulator and in sheep. In the flow simulator, captured emboli firmly adhered to the filter wire and didn't disintegrate upon impact. Thus, in humans, captured embolus disintegration upon impact is probably unlikely. The sheep study showed that autologous captured thrombo-emboli, after 3 weeks, either completely regressed or did not progress. In all cases, no obstruction of blood flow was observed. In IVC filters, at 6 months, 60% of captured emboli regress and 30% do not progress, irrespective of heparin administration [23]. Accordingly, it is likely that in longer observation periods (>30 days) most emboli captured by the CCA filter will either resolve completely or regress.

Ischemic strokes in AF patients are most often of embolic origin. Emboli emerging from the heart or large arteries may lodge in cerebral arteries and cause an infarct. The size of the infarct and consequent brain damage are related to embolus size. In AF patients, 80% of strokes are either total or partial anterior circulation strokes [24] caused by occlusions of the main branches of the carotid artery. In a large majority of cases these arteries exceed 1.5 mm in diameter [25–27]. Because an embolus of a certain size is likely to occlude an artery of the same size, a permanent bilateral carotid filter excluding emboli exceeding 1.5 mm in size may potentially reduce the risk of major stroke in the anterior circulation.

Potential stroke-producing emboli have heterogeneous content. Emboli emerging from aortic and large vessel atheromatous plaques likely include cholesterol and calcium. These emboli will not be fully affected by the fibrinolytic system but are still subjected to the high shear stresses of carotid flow and will therefore likely adhere over time to the vessel wall. Of course, these data should all be viewed as hypothesis-generating, as the true safety and efficacy of this CCA filter concept can only be determined by clinical testing in patients.

To this point, the first-in-human clinical experience with this CCA filter was recently published. In this 3-center, non-randomized, clinical trial of AF patients unsuitable for anticoagulation, bilateral CCA filter placement was successful in 23/25 (92%), and unilateral placement successful in 1 additional patient. There were no major device/procedure related major adverse events. While device efficacy cannot be concluded from such a small cohort, it was striking that there was evidence that the filter captured emboli in subset of patients. *In toto*, this first experience in humans was consistent with the pre-clinical outcomes of the present report. The intended users of the CCA filter are AF patients at high stroke risk who are treated with OAC; the sheep and human studies showed that the implant is safe with anti-platelets therapy alone and thus, may be safe in AF on OAC and during OAC interruptions (*i.e.* surgery, GI bleeding, *etc.*). Recently, enrollment commenced in the *CAPTURE 2* multicenter non-randomized clinical trial (NCT 03892824). In this larger feasibility and safety study, bilateral CCA filter placement is being employed as adjunctive embolic stroke prevention in high stroke risk AF patients while also taking oral anticoagulants. A randomized efficacy trial (*INTERCEPT*) is planned to compare OAC therapy with OAC therapy plus bilateral carotid filter placement with a primary efficacy endpoint of ischemic stroke.

5. Conclusion

Testing of the CCA filter *in vitro* and *in vivo* (*ovine* model) suggests that it is feasible and safe, and that it has the potential to reduce embolic stroke in high-risk AF patients. These data provide a scientific basis for clinical trials in humans.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2020.05.031.

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Disclosures

AN, SB, YD and EK are employees of Javelin Medical Ltd. GS and OY are co-founders and consultants of Javelin Medical Ltd. VYR reports having received stock options from Javelin Medical Ltd. He also has conflicts with other companies not related to this manuscript; a comprehensive list is in the Supplement.

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