

Bionic eye: a glance at the argus ii retinal prosthesis

Abstract

The Argus II retinal prosthesis is a promising new artificial vision restoration technology that, after years of extensive research, is now being implemented on a commercial basis. It is currently the only retinal implant to be approved by the Food and Drug Administration (FDA), Health Canada and the Conformité Européenne. As of now, it is strictly indicated for patients with retinitis pigmentosa and a history of prior useful vision that has worsened to the point of bare light perception or no light perception vision in both eyes. It utilizes an electrode array to stimulate residual retinal ganglion cells, which relay through the visual processing system to the visual cortex and allow the patient to perceive spatial and temporal patterns of lights. The largest prospective multi-center clinical study involving the Argus II implant found that patients demonstrated significant visual improvement as measured by performance on square localization, grating visual acuity and direction of motion tasks. Recipients also exhibited functional visual improvements as assessed by a "door task", "line task" and the Functional Low Vision Observer Rated Assessment (FLORA). This was noted for up to three years following implantation of the device. Both in the research and commercial setting, the Argus II technology has proven to be incredibly promising. Ongoing research is directed at improving the existing Argus II technology, developing next-generation devices and expanding indications of vision restoration to those who do not currently meet Argus II indications.

Keywords: argus II, retina, retinitis pigmentosa, epiretinal, prosthesis

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Abbreviations: FDA, food and drug administration; CE, conformité européenne; USC, university of southern california; VPU, visual processing unit; FLORA, functional low vision observer rated assessment; AMD, age-related macular degeneration

Introduction

The endeavor to artificially restore vision began in 1929 when Othfrid Foerster reported that electrical stimulation of the occipital cortex caused a subject to see a phosphene (a spot of light produced by direct stimulation of the visual system).¹ Further steps were taken in 1956 when Graham Tassiker implanted a light sensitive selenium cell behind the retina of a blind patient, transiently restoring light perception capabilities.^{2,3} These first steps laid the foundation for the success of present-day artificial retinal implants. Retinal implants can be classified according to their location as epiretinal (tacked to the retinal surface) or subretinal (between photoreceptors and RPE). The Argus II epiretinal prosthesis (Second Sight Medical Products, Inc., Sylmar, CA) is currently the only retinal prosthesis approved in the United States by the Food and Drug Administration (FDA) or approved by Health Canada. In Europe, the Argus II as well as the Alpha IMS (Retina Implant AG, Reutlingen, Germany), a light-sensitive subretinal implant, have received the Conformité Européenne (CE) mark.^{4,5} Some other retinal implants still in development or clinical trials include the Boston Retinal Implant,⁶ the Epi-Ret 3,^{7,8} and Intelligent Medical Implants.^{4,9} Other vision restoration implants in their early stages include neurotransmitter based retinal prostheses, cortical prostheses that directly stimulate the visual cortex and photovoltaic cell-based devices.¹⁰⁻¹²

The argus II retinal prosthesis

The Argus II, 60-electrode implant, whose technology and development was pioneered by Mark Humayun, MD, PhD, was first implanted in clinical trials at the University of Southern California

(USC) in 2007. It is the next generation device following the 16-electrode Argus I, which, starting in 2002, was placed in 6 subjects on a research basis also at USC. The Argus II retinal prosthesis consists of a wearable external component and a surgically implanted component. The external component is comprised of glasses, a video processing unit (VPU) and a wired-cable (Figure 1). Figure 1 External (wearable) components of the Argus II retinal prosthesis. Left: Illustration of full external component when worn. It consists of glasses with a small camera in the nasal bridge, a video processing unit (VPU) and a wired cable transmitter containing a radio frequency coil. Right: Photo of actual external apparatus as previously described (Image courtesy of Second Sight Medical Products, Inc.). The implanted component is comprised of a receiving coil and an electronics case secured to the eye in the manner of a scleral buckle as well as a 60-electrode array, which is fastened to the retina with a retinal tack (Figure 2).

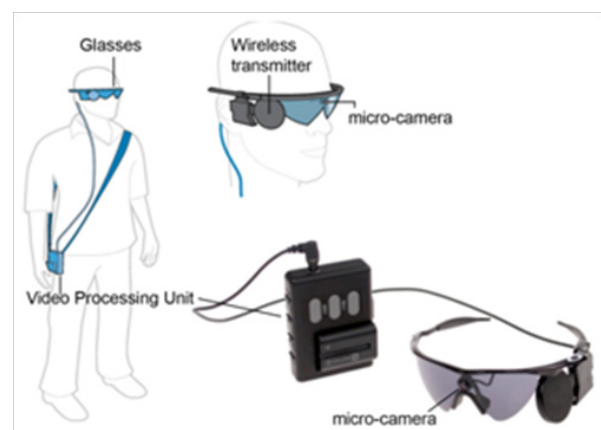


Figure 1 External (wearable) components of the Argus II retinal prosthesis.

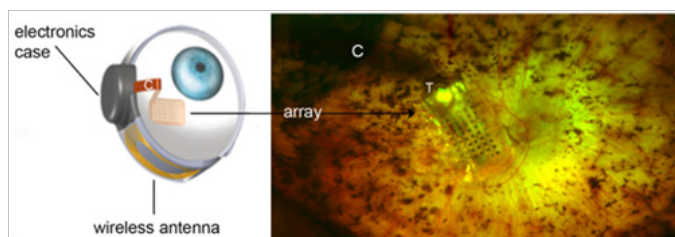


Figure 2 Internal (implanted) components of the Argus II retinal prosthesis.

Figure 2 Internal (implanted) components of the Argus II retinal prosthesis. Left: Illustration shows orientation of implanted components around the eye, including the electronics case and wireless antenna receiving coil secured similar to a scleral buckle and the cable (C) that terminates at a 60-electrode array secured via retinal tack (Image courtesy of Second Sight Medical Products, Inc.). Right: Scanning laser ophthalmoscope image shows the 60-electrode array fastened by retinal tack (T) to its correct position over the macula. The glasses hold a miniature video camera in the nasal bridge that transmits images to the VPU, which in turn converts the images into data that can be sent to the internal electronics package. This data stimulates the electrode array to emit small electrical pulses that excite remaining viable inner retina cells, including ganglion cells. These artificially stimulated retinal ganglion cells then transmit signals through their axons to the lateral geniculate nucleus and on to occipital cortex, which perceives light patterns. Finally, patients then piece together these light patterns to create vision.

Clinical trials

In 2009, the FDA approved the Argus II as a Humanitarian Use Device, a designation aimed at treating patient populations of fewer than 4,000 individuals per year in the U.S. By receiving this approval, the Argus II demonstrated its safety as well as, on a reasonable basis, probable benefits outweighing risks including injury or illness. In the largest prospective, single arm, unmasked, multicenter Argus II study, 30 subjects (9 female, 21 male; mean age 58, range 28-77) from 10 medical centers (6 in the U.S. and 4 in Europe) were implanted with the Argus II on a research basis prior to FDA-approval.¹³ 29 were diagnosed with retinitis pigmentosa and 1 was diagnosed with choroideremia. 29 had bare light perception vision, while 1 had no light perception. Subjects served as their own control (device on versus off). End-points for this trial took into consideration the significant vision loss in this patient population, which precluded accurate assessment of visual acuities by conventional methods, such as visual acuity charts. Visual acuity was assessed with three objectives metrics-square localization, direction of motion and grating visual acuity. The square localization test assessed the ability to localize a white square on a black screen (Figure 3A). The direction of motion test assessed the ability to determine the direction of motion of a white line moving across a black background (Figure 3B). The grating visual acuity test assessed the ability to identify the orientation of white and black bars of progressively narrowed widths (Figure 3C).¹³ In alter study of 21 Argus II subjects, patients were also asked to identify white letters (individual letters and small words) projected over a black background (Figure 3D).¹⁴

Functional vision was evaluated with a “door task” that tested whether the patient could locate a large piece of black felt hung on a white wall to simulate a doorway (Figure 3E) as well as a “line task” that tested the patient’s ability to follow a white line on the floor to simulate the straight lines of a crosswalk or sidewalk (Figure

3F). Performance on these tasks was evaluated at 3,6,12,18 and 24 months post-implant. Patients performed significantly better on the door task at all points except 12 months with the device on vs. off. Additionally, they performed significantly better on the line task at all points with the device on vs. off (using repeated measure Analysis of Variance). Figure 3 Endpoints evaluated in the Argus II clinical trials. A-D: Visual acuity metrics. E-F: Functional vision metrics. Results showed that the patients performed better in all six categories with the device on vs. off (Images courtesy of Second Sight Medical Products, Inc.). Additionally, this study employed the Functional Low Vision Observer Rated Assessment (FLORA) during which an independent low vision specialist was asked to observe and create a narrative outlining the patient’s use of the device in his/her own home environment.

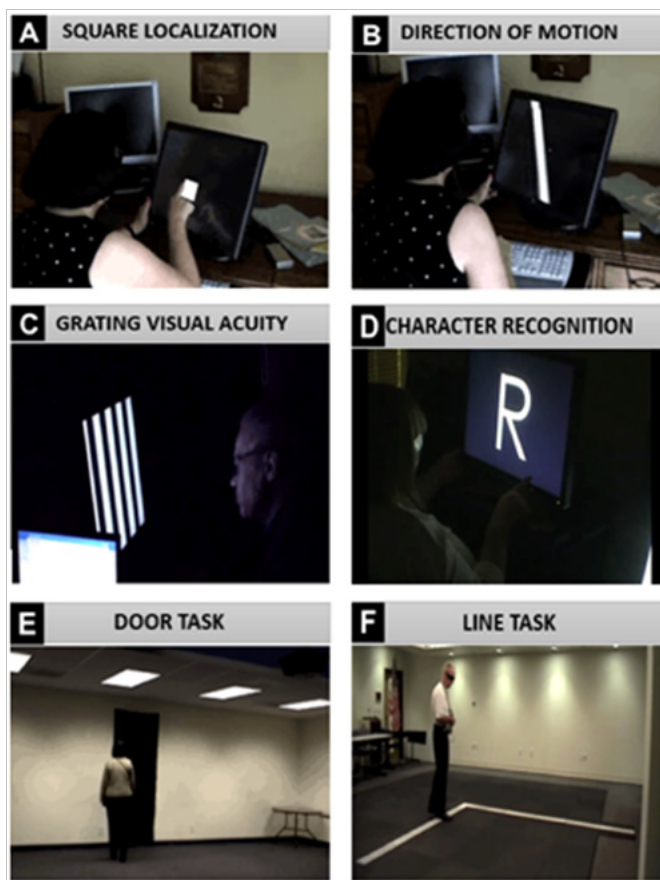


Figure 3 Endpoints evaluated in the Argus II clinical trials.

At up to three years follow-up, improved patient performance with the system on versus off was noted with respect to all three of the aforementioned visual acuity metrics. 96% of subjects performed better on square localization with the system on vs. off and 57% performed better on direction of motion ($p < 0.05$). Of note, 27% of patients regained a measurable visual acuity (grating visual acuity of 2.9 logMAR) with improvement up to 1.8 logMAR (equivalent to 20/1262).¹³ Some subjects were also able to identify letters as small as 0.9 cm and a few patients could correctly identify two, three and four letter words.¹⁴ Patients also exhibited improved performance on the functional vision tasks, as well as subjective improvements in sorting laundry, staying on a crosswalk, locating doors and windows, following lines and edges, detecting/avoiding obstacles, locating/tracking people and most importantly feeling more socially connected.

Using the FLORA assessment, an independent specialist observed that 77% of subjects had a positive effect from the Argus II, while 23% had no positive effect; no patients had a negative effect. Safety metrics verified that there was no permanent impairment, no additional loss of remaining native vision and no mechanical failure of the Argus II. Surgery-associated complications were noted in 9 of 30 patients including hypotony, conjunctival erosions and endophthalmitis, all of which were successfully addressed except in one patient with conjunctival erosion resulting in removal of the Argus II.¹³ Many of these complications were attributed to early experiences with the Argus II and most (82%) occurred within the first 6 months post-implant; improvements in the implantation procedure and the Argus II device have resulted in improved adverse event profiles, as evidenced by the fact that subjects enrolled later in this study suffered fewer adverse events (4 events in 2 subjects who enrolled later vs. 13 events in 7 subjects who enrolled earlier).^{14,15}

Candidates for the argus II

The Argus II is intended to restore rudimentary functional vision to patients with a significant vision loss. Per FDA guidelines, it is suitable for use in adults (age 25 years or older) with retinitis pigmentosa and a history of prior useful vision that has worsened to the point of bare light perception or no light perception vision in both eyes. The patient must be aphakic or pseudophakic and the natural lens, if present, would need to be removed during the implantation procedure. Contraindications include comorbidities that would prevent the implant from functioning properly (e.g. cortical blindness, optic nerve disease, history of retinal detachment, retinal vascular occlusion, trauma, severe strabismus). Other contraindications include conditions that would interfere with successful implantation of the Argus II such axial length <20.5 mm or >26 mm (given the fixed intraocular cable length), thinning of the conjunctiva and conditions that prevent visualization of the implant such as corneal opacities. The Argus II is additionally contraindicated in patients prone to rubbing their eyes as well as those with devices implanted in the head such as cochlear implants.

Surgical technique and postoperative follow-up

The implantation procedure for the Argus II was refined to incorporate techniques including those familiar to most trained vitreoretinal surgeons. The implant is secured to the eye wall much like an encircling scleral buckle. The 60-electrode array is then passed into the vitreous cavity via a 5.5 mm sclerotomy. A retinal tack is used to fasten the implant to the outer wall coats including retina-choroid-sclera. The tack is placed to center the array over the macula. The electronics case and suture tabs are covered by a patch graft. Finally, the overlying conjunctiva and tenon's capsule must be closed. Other skills that may be employed depending on the circumstances include crystalline lens removal, anchoring of suture tabs and vitrectomy. The patient is regularly followed to monitor the development of any postoperative complications, with special attention paid to conjunctival erosion, endophthalmitis and hypotony. Standard eye drops are administered and steroid and antibiotic therapy is limited to the perioperative period only.

Within weeks of surgery, the VPU is programmed to optimize each electrode per the patient's residual stimulation thresholds. Following optimization, the external glasses are activated and the electrode ray is stimulated. The VPU is customizable and programmed with adjustable settings to maximize visualization of high contrast items as well as edge detection, for example. After the optimization process is

complete, the patient receives low vision rehabilitation and orientation and mobility training coordinated with a low vision specialist and occupational therapist. This rehabilitation is an intensive process, which begins over the first several months following implantation but involves ongoing dedication and learning in order to most effectively use their new implant.

A patient's perspective

A 66 year old patient began losing eye sight over 30 years ago, at which time he was diagnosed at the Duke Eye Center with retinitis pigmentosa. In the absence of any medical treatment to prevent this vision loss, his eye sight gradually but progressively deteriorated. For about ten years, he could not identify whether ambient lights were on or off. One of his favorite activities was listening to the July 4 fireworks with his youngest granddaughter sitting on his lap and he dreamt of one day being able to again "see" the flashes of fireworks. Having understood the limitations of the Argus II as well as the postoperative training he would need to undergo to maximize its utility, he was eager to pursue any chance of improvement in his vision. Following successful surgical implantation, this patient began the journey of visual rehabilitation. Three weeks after surgery, after his VPU had been optimized, his device was turned on, allowing him to visualize phosphenes (light flashes in response to controlled electrical stimulation of the retina as opposed to light actually entering the eye) for the first time in years. One day later his wife noted, "As we were driving home, he turned the device on. He was able to distinguish where the streetlights were, a lit billboard and headlights as they came our way. It was truly amazing!" One of the first major changes he noticed was with lamps in his home: "Before the Argus II, I could not tell if a lamp in the house was on or off without burning my hands. Now with the Argus II, I can go around and turn lamps off that are on. That is pretty functional for me!" Several weeks into his device, he tried to play Velcro darts with his granddaughter. As his wife describes, "I told him he should put on his glasses and see if he could tell where the dart board was. He put on his glasses. Shocker! He found the dartboard and started playing. He rarely missed. That's about as much fun as he has had in a long time playing a game. He wanted to try it again tomorrow and the next day and the next day! To be truthful, I was kind of surprised that he could see it as well as he did. But the darts didn't lie. He did well!" With continuing rehabilitation, this patient has continued to learn how to more effectively utilize his device. He enjoys being able to locate doorways and windows, find and touch his wife's and grandchildren's faces and improve navigation and confidence with social interaction. And perhaps most importantly for him, when his first July 4 approaches, he should expect to be able to see the flashes of fireworks. His experiences in a new world augmented by vision stimulation have just begun.

Future directions

The approval of the Argus II represents the ability to restore vision in those whose vision was previously thought to be permanently lost. Retinal implants, while they do not restore natural vision and are now only approved in cases of retinitis pigmentosa, have certainly been promising in their early stages of development.

Ongoing research is dedicated towards development and refinement of technology to improve safety and durability as well as image resolution. Next generation glasses may incorporate advancements such as eye tracking sensors to enhance recipient's identification of obstacles. Increased visual resolution may be achieved through modifications to improve existing physical electrodes and create

virtual electrodes to increase the number of perceived “pixels.” Color stimulation is in the early phases of research, but preliminary trials with the Argus II are promising, with the ability to simulate color vision on different electrodes in a reproducible fashion (personal communication, Second Sight Medical Products, Inc). Additionally, enhanced video processing based on ongoing improved understanding of the nuances of visual encoding pathways could improve visual output. One advantage of the Argus II design is the external location of the VPU and any of these updates would likely constitute a simple software update of the external computer without need for further surgical intervention.

Progress is being made to explore indications in other ocular diseases like age-related macular degeneration (AMD), the leading cause of blindness in the western hemisphere,¹⁶ for which trials are under way to determine the utility of Argus II for advanced geographic atrophy. If successful, indications for the Argus II could be expanded to include the wet form of AMD without active angiogenesis.

This application of artificial restoration technology could similarly be expanded to additional new patient populations if it were able to bypass dysfunctional parts of the visual processing system in affected patients. With that in mind, Second Sight is also currently developing the Orion Cortical Prosthesis, which is implanted in the visual cortex itself, thereby circumnavigating the optic nerve, tract and radiations. Unlike the Argus II, the electrode array in the Orion is a cortical array rather than a retinal array. Such a technology could then be used in those with pathology of the inner retina such as retinal artery occlusions, those with panretinal pathology such as trauma, infection, or retinal detachment and those with optic nerve pathology as in glaucoma. In addition to the Argus II, there are several other retinal prostheses in development that could be promising in their own right. Currently, the Argus II and the Alpha IMS are the only two devices approved by regulatory organizations. The Alpha IMS is the only such device that captures images using a multi photodiode array.^{4,5} Additionally, it has a significantly larger electrode array compared to the Argus II and other devices (1500 photodiodes vs. 60 electrodes for Argus II,^{4,5} 100 electrodes for Boston Retinal Implant,⁶ 25 electrodes for Epi-Ret-3^{7,8} and 49 electrodes for Intelligent Medical Implants.^{4,9} These electrodes on the Alpha IMS are significantly smaller than those for the other devices (15x30 μm vs. 200 μm for Argus II,^{4,5} 400 μm for Boston Retinal Implant,⁶ 100μm for Epi-Ret-3^{7,8} and 100 to 360 μm for Intelligent Medical Implants.^{4,9} It should be stressed that each implant represents differing technologic approaches that should not be directly compared. Differences in performance or functional outcomes should not be inferred based on technical differences but should await prospective direct comparison.

Conclusion

The approval of the Argus II for commercial implantation has ushered in a new era of hope and promise for restoration of vision. It has proven to be a feasible and safe long-term solution for vision restoration in the patients with retinitis pigmentosa. The early success of the Argus II has also spurred new research endeavors to improve on the existing hardware as well as develop novel devices to optimize the quality of life enjoyed by recipients of these implants. The hope is that in the future these devices will be more broadly applicable to enable as many patients as possible to reap their benefits.

Acknowledgments

None.

Conflicts of interest

Paul Hahn, MD, PhD is a consultant with Second Sight Medical Products. Mark Humayun, MD, PhD is a consultant, equity owner and holds patents with Second Sight Medical Products, from whom he also receives lecture fees and grant support.

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