Minimally invasive surgical techniques that leave the sclera and conjunctiva intact, collectively known as MIGS (minimally or micro-invasive glaucoma surgery), are playing an increasingly important role in the treatment of glaucoma.

Current glaucoma treatment guidelines suggest a graduated approach of increasing invasiveness as the disease progresses, starting with medical therapy, refractory patients commonly progress to laser trabeculoplasty and from there to filtration surgery. However, between those glaucoma patients who respond well to non-incisional treatments, like topical medication and laser trabeculoplasty, and those patients who require filtration surgery to achieve a low target IOP, there are a range of patients who don’t fit neatly into either category but who may respond well to MIGS.

“What distinguishes MIGS from traditional glaucoma surgery is that it is a much, much safer and often more physiologic type of procedure. It is therefore something that we’re more comfortable using in patients earlier in the disease and potentially also in patients who are at a higher risk for more complications from standard trabeculectomy-type surgery. And that is probably the biggest hallmark of MIGS, it is an ultra-safe procedure,” said Ike Ahmed MD, University of Toronto, Toronto, Ontario, Canada, who originated the MIGS acronym.

The MIGS techniques include a range of ab interno implants, and an electric microcautery device. They are designed to provide an outlet for aqueous into the venous system by way of Schlemm’s canal and the collector channels, through the suprachoroidal space, or through a subconjunctival bleb. The procedures are performed through small incisions and with gonioscopic visualisation. They are primarily indicated in patients who have visually significant cataracts as well as glaucoma.

“Restricting the use of MIGS to cataract patients was the regulatory pathway that was selected with the procedures and MIGS procedures work well in terms of synergy with cataract surgery so it’s a nice adjunct there. But we are currently also involved in a number of studies where we are looking at these devices for use in patients who are phakic and not undergoing cataract surgery. That is the next step with MIGS,” said Dr Ahmed.

The MIGS techniques generally reduce IOP to a lesser degree than trabeculectomy but by an amount that may nonetheless be sufficient to prevent optic neuropathy progression in some glaucoma patients. The MIGS techniques appear to have a better risk profile than trabeculectomy, which for several decades has been the gold standard for the treatment of glaucoma patients in whom topical medication controls IOP inadequately.

Two of the most serious complications of trabeculectomy are hypotony maculopathy, occurring most commonly in the early postoperative period, and bleb-associated endophthalmitis, which tends to occur much later. In eyes that have undergone trabeculectomy, the reported incidences of hypotony maculopathy range from 1.3 per cent of 18 per cent. Endophthalmitis after trabeculectomy has a reported incidence of 7.5 per cent at five years. The use of antifibrotic agents appears to increase the risk of both complications.

Timely intervention to raise IOP to a safe level will preserve the vision of most eyes with hypotony maculopathy, but if the condition goes undetected it will result in scar formation in the chorioretinal wrinkling that the hypotony causes, with a permanent reduction of visual function as a result.

The visual outcomes of bleb-associated endophthalmitis are almost universally

**Tube, or not tube?** Because of trabeculectomy’s potential complications and because of the limitations and the side effects of topical medications, numerous teams of investigators around the world have since developed alternative surgical techniques for lowering IOP that are less invasive and have a better safety profile than conventional filtration surgery.

They include laser trabeculoplasty – which current guidelines accept as an intermediate treatment option between topical medication alone – and filtration surgery – and a broad range of drainage implants. Among the newest in the latter category are several implants designed for use in MIGS.

The older generation of drainage implants, namely the Baerveldt, Ahmed and Molteno tubes consist of a plate placed subconjunctivally from which a drainage tube that is inserted through the sclera into the anterior chamber. These devices essentially drain aqueous out of the eye into subconjunctival reservoirs created by external plates.

The traditional indications for the tube implants have been for eyes that seemed likely to have unsuccessful results with trabeculectomy, as in cases where there is extensive scarring from previous surgery. However, the past decade or so has seen an increased adoption of the device, for example, a survey of American Academy of Ophthalmology members showed that the proportion of their surgeries using tube implants rose from 17 per cent in 1998 to 54 per cent in 2008. (Desai et al, Ophthalmic Surg Lasers Imaging. “Practice preferences for glaucoma surgery: a survey of the American Glaucoma Society in 2008”, 2011 May-Jun;42(3):202-8).

In Tubes Versus Trabeculectomy Study (TVTS), trabeculectomy resulted in greater IOP reduction but also significantly more complications in the early postoperative period than did implantation of the Baerveldt device (37 per cent vs. 21 per cent, P = .012). The cumulative probability of failure during five years of follow-up was 29.8 per cent in the tube group and 46.9 per cent in the trabeculectomy group (P = .002). The rate of reoperation for glaucoma was nine per cent in the tube group and 29 per cent in the trabeculectomy group (P = .025) (Gedde SI, et al, Am J Ophthalmol “Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up”, May 2012;153:5:789-803 [782]).

On the other hand both techniques had similar rates of late postoperative complications making tube shunts less attractive to use in mild to moderate glaucoma.

**MIGS, the new kid on the block** In contrast, use of the new MIGS devices involves only a small amount of disturbance of ocular tissues and consequently has much fewer side effects.

The iStent (Glaukos Corporation[see Figure 1]) and the Hydrus (Ivanits [see Figure 2]) and the Trabectome® (Neomedix) are all designed to direct aqueous out through Schlemm’s canal. They therefore have a mechanism in common with some more invasive ab externo forms of a Schlemm’s canal surgery, such as viscocanalostomy and cananoplasty. They also share an inherent limitation with those techniques in that they cannot bring pressures below episcleral venous pressure 12 mmHg. On the positive side, the techniques do not result in the creation of a bleb.

The iStent is composed of nonferromagnetic titanium and is designed to provide a channel for the outflow of aqueous directly from the anterior chamber to Schlemm’s canal, bypassing the trabecular meshwork. The ab interno device was approved by FDA in 2012 for use with cataract procedures.

The FDA trial showed that among patients receiving the implant while undergoing cataract procedures, 73 per cent maintained an IOP of 21 mmHg or lower without medication at 12 months follow-up. That compared to only 50 per cent of those who underwent cataract surgery alone.

More recent research by Ike Ahmed MD and his associates demonstrated that two stents can consistently reduce IOP to less than 15 mmHg (G Belovay et al, J Cataract Refract Surg. “Using multiple trabecular micro-bypass stents in cataract patients to treat open-angle glaucoma”, 2012 November; 38:1911-1917).

Manfred Tetz MD, Berlin, reported similar results at this year’s ESCRS Winter Meeting using the new collar-button design of the iStent. At 12 months postoperatively, mean IOP was 14.5 mmHg and the mean number of ocular hypertensive medications patients needed decreased from 1.8 medications preoperatively to 0.3 medications or less at all postoperative time periods.

The manufacturers of the Hydrus implant describe the device as an intracanalicular scaffold. It is designed for placement into Schlemm’s canal from the inside of the eye. It therefore resembles in design and purpose the Stegmann canal expander, a device implanted by an ab externo approach. However, unlike the ab externo device, the Hydrus has a special injector system and does not require any disturbance of scleral or conjunctival tissue.

In a study Dr Tetz presented at the XXX Congress of the ESCRS in Milan last year, patients with mild to moderate open-angle glaucoma who were concurrently undergoing cataract surgery underwent implantation of the Hydrus device. At 12 months, washed out IOP was 15.5 mmHg, a decrease of 9.1 mmHg from preoperative washout values.

“The results are encouraging. But one little thing remains uncertain with all internally placed implants, did I really hit Schlemm’s canal? And did I put the implant first full-length inside Schlemm’s canal? In most cases with modern implants with the Hydrus and the iStent you’re reasonably sure, but with the Grieshaber Stegmann canal expander you implant it from the outside after opening up the canal, so you’re 99 per cent sure that you really placed it in Schlemm’s canal,” Dr Tetz said.

The Trabectome opens access to Schlemm’s canal by ablating a portion of the trabecular meshwork of the eye with an electro surgical hand piece. It received FDA approval in 2004. In a prospective trial by the Trabectome Study Group involving more than 300 patients, the mean IOP fell from preoperative values of 20.0 mmHg to 15.5 mmHg at one year’s follow-up. The mean number of drops patients needed fell from 2.65 ± 1.13 at baseline to 1.29 at one year. (BA Francis et al J Cataract Refract Surg. “Combined cataract extraction and trabeculectomy by internal approach for coexisting cataract and open-angle glaucoma. 2008 Jul;34(7):1096-103).

The CyPass (Transcend Medical, Menlo Park, Calif.) uses a different approach, directing the outflow of aqueous into the suprachoroidal space. The CE Mark approved device consists of a tube 6.35mm in length and with an outer diameter of 0.51mm composed of a polyimide material. Like the other MIGS implants it is placed in the eye using an ab interno approach positioned in a superciliary clef created with the implantation device.

The one-year results of the CyCYLE study presented at the annual AAO Meeting in Chicago last year revealed that implantation of the device reduced mean IOP by 35 per cent to 16.3 mmHg and a reduced mean medication usage by half. What remains to be seen is whether the device will continue to work over the long-term, Dr Tetz said.

“My current opinion is that the suprachoroidal approach doesn’t seem to work well enough in the long-term. I think with a number of studies we have good one-year data and you see that most of the devices close off after one and a half years,” he added.

The Xen microstentula implant, AqueSys, is an investigational device delivered through an ab interno incision to create an external subconjunctival filtration pathway, similar to trabeculectomy. It is composed of a soft
I find that trabeculectomy using the Moorfields Safer Surgery System is probably my surgical therapy of choice particularly in those who need very low pressures, Peng T Khaw MD, PhD.

Moorfields Eye Hospital London, UK, told EuroTimes in an interview.

“It is true that trabeculectomy gets a lot of bad press. It’s not perfect, it requires too much time and skill to do. It is not the solution to glaucoma and in the long run we need much better things to sort out glaucoma. However, I find that trabeculectomy using the Moorfields Safer Surgery System is probably my surgical therapy of choice particularly in those who need very low pressures,” he said.

He explained that the Moorfields safer surgery system for trabeculectomy greatly reduces the incidence of hypotony in the early postoperative through the use of adjustable sutures (Figure 3). It also reduces late postoperative bleb-associated complications by creating a broader more diffuse filtration area (Figure 4).

He added that an audit performed also at Moorfields Eye Hospital by Hari Jayaram and Debbie Kamal showed that performing trabeculectomy procedures with lower target IOPs of around 10.0 mmHg appeared to stabilise the optic neuropathy and visual field status of patients with normal tension glaucoma whose condition was previously progressing despite well-controlled IOP.

He noted furthermore, that accurate assessment of the comparative value of MIGS techniques must await longer term follow-up than has yet been reported.

“All of the implants in the past have one problem they all failed for one reason - the body reacts to what you’ve done and tries to close it off. Whether it’s an iStent, or a Hydrus or a Cypass, they’re all susceptible in the long-term to being blocked off by scarring. There have been other suprachoroidal shunts, they all are susceptible to scarring and I’m pretty sure even the Schlemm’s canal ones are going to get some scarring,” Dr Tetz said.

Clive Peckar FRCOphth UK told EuroTimes he does not agree with Peng Khaw’s assessment regarding the long-term efficacy of stents in Schlemm’s canal. He pointed out that studies using gonioscopic imaging of early prototype intracanicular devices show that they continue to maintain the patency of Schlemm’s canal for over 10 years, due to the intrinsic fibrinolytic activity within Schlemm’s canal. (See Figure 5, Gonioscopic view of 3mm polyimide trans-ostial stents,10 years after surgery, IOP: 40-15 mmHg).

He pointed out that the ab externo approach, used in canaloplasty, permitted the atraumatic dilation of Schlemm’s Canal and it’s collector channels to be performed prior to the insertion of intracanalicular stents, such as the Stegmann Canal Expanders (Ophthalmos). However, the ab interno approaches, such as the Hydrus and the iStent, are more prone to be blocked by fibroses, induced by canal endothelial trauma, following insertion into the undilated 25 micron deep “slit” that is Schlemm’s canal. As with all Schlemm’s canal surgeries they are limited by episcleral venous pressure, in their IOP-lowering capability.

He also pointed out that over the 16 years he has been performing Schlemm’s Canal Surgery, the only consistent and reproducible way of dilating the canal and collector channels atraumatically, was to use the ab externo approach, and that there is some evidence to suggest that, without dilatation, ab interno devices might only function optimally when positioned opposite large collector channel ostia.

Dr Peckar noted that clinical studies with the Stegmann Canal Expanders” began in 2010. They have an additional advantage, over the tension suture canaloplasty technique, in that they do not depend on Schlemm’s canal being catheterised throughout its complete circumference. He added that there is now some evidence of a further lowering of IOP around two years after surgery, related to increased permeability of the Trabecul Meshwork, due to the presence of the Expanders (See Figure 6, stream of red blood cells passing through the ribs of Stegmann Canal Expander two years after surgery, IOP: 39-16 mmHg).

Glaucoma treatment at a crossroads | Regarding the future of glaucoma treatment, Dr Ahmed noted that, developing in tandem with MIGS techniques, there have been a range of new technologies for delivering glaucoma medication to the eye in ways that may reduce irritation and may also be less reliant on a patient’s willingness to adhere to their prescribed regimens. That could in turn delay progression and the need for surgery.

“There is some really interesting and exciting work being done with drug delivery and sustained release systems including ocular surface sustained-release inserts, punctal plugs, subconjunctival...
injections anterior chamber drug pellets and intravitreal injections, all with different long-lasting medications. By delivering the medication to the site of action they reduce the need for compliance and adherence and reduce side effects.”

In contrast, Dr Tetz told EuroTimes he foresaw an era when IOP-lowering medical therapy would be increasingly replaced by largely atraumatic surgical techniques. He pointed out that medical therapy can be quite invasive in the way it damages tissue during long-term use. Moreover, selective laser trabeculoplasty is not as selective as its name would suggest, since it causes micro-scarring to Schlemm’s canal and therefore reduces the efficacy of subsequent Schlemm’s canal surgery.

“The safer and more controlled surgery becomes, the more I see it as taking over parts of the drop market. Medication will still have a role but it will be more and more directed towards neuroprotection,” Dr Tetz said.

Dr Khaw said that he thought that what glaucoma surgeons should strive for is a 10-minute technique that will reduce IOP to 10 mmHg for at least 10 years.

“If we meet that challenge it could save millions of people around the world from going blind so that’s our challenge for the next decade,” Dr Khaw asserted.

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COMING SOON IN SEPTEMBER EUROTIMES...
Gene therapy for inherited retinal disease
It has been estimated that one in 150 people in developed regions have severe visual impairment due to a retinal condition, ranging from extremely rare “orphan” hereditary retinal degenerative diseases to diabetic retinopathy.

Individuals diagnosed with retinitis pigmentosa (RP) or Leber’s congenital amaurosis have a poor visual prognosis and potential treatments are limited. For decades scientists and ophthalmologists have sought ways to stop the progression of these diseases though, until recently, without success. In the past five years, gene therapy has emerged in ophthalmology as an exciting new approach in the treatment of many retinal disorders that are considered incurable.

Nearly 30-plus trials are currently under way around the world into degenerative retinal diseases such as Leber’s, Stargardt’s, RP, Usher’s syndrome and others. The story will look at the more promising of these, outline the latest results, discuss delivery methods and potential problems/obstacles to progress, and likely future avenues of research.