Editorial

Navigating a new direction in micro-invasive glaucoma surgery: results from the COMPASS trial

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Recent innovations and technological advances have ushered in a new era of surgical approaches to glaucoma management. Our options have expanded beyond traditional incisional glaucoma surgery (i.e., trabeculectomy and tube shunts) to include newer procedures that can be implemented earlier in patients with milder disease. Many of these recently introduced operations can be classified as micro-invasive glaucoma surgery (MIGS), for which five defining criteria have been proposed: an ab interno approach; minimal tissue trauma; at least modest efficacy; high safety; and rapid recovery (1). Candidates for currently available MIGS are generally those with early glaucoma whose disease does not require very low intraocular pressure (IOP) to retard progression and/or who may benefit from reduction in medical therapy.

A novel supraciliary micro-stent (CyPass Micro-Stent; Alcon Laboratories, Inc., Fort Worth, TX, USA) is the first MIGS device targeting a pathway other than the trabecular meshwork/Schlemm's canal (TM/SC) to receive approval from the United States Food and Drug Administration (FDA). Indicated for combined use with phacoemulsification cataract surgery in patients with coexistent mild-to-moderate primary open-angle glaucoma (POAG) and cataract, the CyPass Micro-Stent is a 6.35 mm fenestrated polyimide device with a 300-micron internal luminal diameter. Insertion between the scleral spur and ciliary body is performed under gonioscopic guidance through a clear corneal incision using a preloaded guidewire. A controlled cyclodialysis cleft is thus created, promoting aqueous flow from the anterior chamber through the stent's lumen and its fenestrations into the suprachoroidal space.

Vold *et al*. recently reported 2-year safety and efficacy results from the pivotal multicenter COMPASS trial (2), which led to FDA approval of the CyPass Micro-Stent. Patients with POAG and cataract (N=505) were prospectively randomized 3:1 to undergo combined phacoemulsification cataract surgery and CyPass Micro-Stent implantation (micro-stent group; N=374) or phacoemulsification cataract surgery only (control group; N=131). Medication washout was performed before the second baseline visit and at 1 and 2 years postoperatively. Similar mean diurnal IOP (24.4±2.8 mmHg micro-stent group *vs*. 24.5±3.0 mmHg control group, P>0.05) and mean number of glaucoma medications (1.4±0.9 medications micro-stent group *vs*. 1.3±1.0 medications control group, P>0.05) were observed at baseline between the two randomized groups. A greater proportion of micro-stent patients than control patients achieved the primary outcome (≥20% decrease in washed-out diurnal IOP compared to baseline) at 2 years (77% micro-stent group *vs*. 60% control group, P=0.001). A higher percentage of patients in the micro-stent group compared with the control group maintained IOP ≤21 mmHg without medications at 2 years (85% micro-stent group *vs*. 59% control group, P value not reported), and patients in the control group required 3-fold more glaucoma medications than patients in the micro-stent group (0.6±0.8

medications control group *vs.* 0.2±0.6 medications micro-stent group, P<0.001). At 2 years, mean unmedicated IOP was lower in the micro-stent group relative to the control group (17.0±3.4 mmHg micro-stent group *vs.* 19.3±3.3 mmHg control group, P value not reported). Adverse events, including intraoperative hyphema (2.7% micro-stent group *vs.* 0.0% control group, P=0.07), iritis (8.6% micro-stent group *vs.* 3.8% control group, P=0.08), hypotony (IOP <6 mmHg; 2.9% micro-stent group *vs.* 0.0% control group, P=0.07), and IOP elevation (≥10 mmHg above baseline; 4.3% micro-stent group *vs.* 2.3% control group, P=0.43), were transient. Micro-stent-related complications, such as cyclodialysis cleft >2 mm (N=7), obstruction due to peripheral anterior synechiae (N=8), malpositioning (N=2), and migration/dislodgement (N=2), were infrequent and not sight-threatening. Additional glaucoma surgery was required in three micro-stent patients and four control patients (details not reported).

Phacoemulsification cataract surgery alone has been shown to lower IOP (3,4). Among eyes in the observation group of the Ocular Hypertension Treatment Study (OHTS), those that underwent cataract extraction (N=63) demonstrated a 16.5% lower IOP than eyes that did not (N=743) for up to 3 years postoperatively (3). Consequently, in order for MIGS devices to be considered effective, they must demonstrate greater IOP lowering when combined with phacoemulsification than phacoemulsification alone. However, to date, randomized controlled trials (RCTs) comparing MIGS devices combined with phacoemulsification to phacoemulsification alone have only been published for the iStent (Glaukos Corp., Laguna Hills, CA, USA), the investigational Hydrus micro-stent (Ivantis, Inc., Irvine, CA, USA), and now the CyPass Micro-Stent. Safety and efficacy data for other MIGS procedures are derived mostly from retrospective studies and uncontrolled prospective case series. The authors of the COMPASS trial are to be congratulated for a well-designed RCT, which includes a phacoemulsification-only group to serve as an appropriate control.

Uveoscleral outflow is driven by a negative pressure gradient between the anterior chamber and suprachoroidal space, which increases with higher IOP (5). Procedures designed to augment aqueous outflow to the suprachoroidal space have been of interest to glaucoma surgeons long before the advent of MIGS. Barkan *et al.* first described a series of 14 ab externo surgically-induced cyclodialysis clefts in 1936 (6). Early cyclodialysis procedures created a free communication between the anterior chamber and suprachoroidal space, analogous to traumatic clefts. It is not surprising that cyclodialysis surgery was subject to inconsistent efficacy with risk for postoperative hypotony and IOP elevation resulting from spontaneous cleft closure, leading to its eventual abandonment. The suprachoroidal space reemerged in recent years as a potential target for newer implants that produce a controlled cleft with more predictable IOP outcomes. The SOLX Gold Shunt (SOLX Inc., Waltham, MA, USA) is an investigational rectangular double-plated fenestrated implant composed of 24-karat gold. The shunt is inserted beneath a scleral flap via an ab externo approach into the anterior chamber (7). Results have been equivocal, with reported failure rates as high as 97% up to 4 years postoperatively (8-10). Histologic studies have confirmed encapsulation of the implant with ingrowth of connective tissue into its fenestrations as a likely cause of failure (11). The ideal suprachoroidal device is one that incites minimal tissue reaction and fibrosis and can be performed via an ab interno approach, sparing the conjunctiva for later surgery if needed. The newer iStent Supra (Glaukos Corp., Laguna Hills, CA, USA) is a 4-mm tube composed of polyethersulfone and titanium that is implanted using an ab interno approach, similar to the CyPass Micro-Stent, and is currently under investigation.

Uveoscleral outflow is not limited by episcleral venous pressure as is outflow through the conventional trabecular pathway, so procedures targeting the suprachoroidal space theoretically have a potential advantage over TM/SC-based procedures. The COMPASS trial was similar in design to, and lends itself to comparison with, the pivotal iStent trial and HYDRUS II trial, which evaluated the trabecular micro-bypass iStent and intracanalicular scaffold Hydrus micro-stent, respectively. The pivotal iStent trial randomized patients with open angle glaucoma and cataract to receive phacoemulsification-iStent (N=117) or phacoemulsification alone (N=123) (12). Unlike in the COMPASS trial, patients did not undergo medication washout. At 1 year, mean IOP was 17.0±2.8 mmHg in the iStent group using 0.2±0.6 medications (12), and remained stable at 17.1±2.9 mmHg on 0.3±0.6 medications 2 years postoperatively (13). The HYDRUS II trial randomized patients to receive either phacoemulsification-Hydrus micro-stent (N=50) or phacoemulsification alone (N=50) (14). Patients who underwent the combined procedure had a 2-year washed-out mean IOP of 16.9±3.3 mmHg, compared with 19.2±4.7 mmHg after phacoemulsification alone (P=0.0093). Despite different device designs and anatomical targets, the Hydrus micro-stent and CyPass Micro-Stent, when

combined with phacoemulsification, produced a similar washed-out mean IOP at 2 years, and delivered a modest additional IOP benefit (of approximately 2 mmHg) over phacoemulsification alone.

The results of the COMPASS trial suggest that although safer than trabeculectomy and tube shunts, the CyPass Micro-Stent appears to have limited efficacy that is comparable to existing TM/SC-based procedures. A postoperative IOP in the mid-to-high teens is likely not sufficient for many patients with moderate-to-advanced and/or progressive glaucoma. Of course, MIGS is intended to fill an as yet unmet need for management options between medical therapy/lasers and traditional incisional glaucoma surgery, rather than to supplant the latter. Perhaps the greatest contribution of the CyPass Micro-Stent (as well as the iStent and Hydrus micro-stent) is in relieving medication burden. Medication-free rates at 2 years in the three pivotal MIGS RCTs were higher with the CyPass Micro-Stent (85% CyPass group *vs.* 59% control group, P value not reported), iStent (61% iStent group *vs.* 50% control group, P=0.036), and Hydrus micro-stent (73% Hydrus group *vs.* 38% control group, P=0.0008) compared with phacoemulsification alone. Reduction in medical therapy could prove useful in patients with early glaucoma who exhibit poor adherence or intolerance to topical therapy, and who do not require very low target IOP.

The niche for MIGS devices is still in evolution, and future generations of MIGS may allow glaucoma surgeons to individualize therapy to each patient across the full spectrum of disease severity and anatomical variation. While initial studies evaluating MIGS were limited by a lack of appropriate control groups, newer, well-designed RCTs like the COMPASS trial offer higher level, albeit early, evidence. Long-term data will help us understand whether late complications, such as fibrosis around the implant, will further limit the efficacy of suprachoroidal devices. The trade-off between safety and efficacy will continue to pose a challenge as new procedures are developed, as optimizing one objective appears to inevitably compromise the other to some degree.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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