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WHAT'S NEXT IN MIGS?

Attempting to achieve subconjunctival drainage with a novel surgical device facilitates outflow while minimizing hypotony.

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Coupled with an improved ability to recognize early warning signs of glaucomatous progression, the continued evolution of the MIGS class has expanded the opportunities for earlier intervention. In many instances, initiating medical therapy in the first line for treatment-naïve patients at risk for progression is no longer the most desirable option. Indeed, as quality of life issues and cost concerns become increasingly important, interventions that obviate the need for the daily instillation of drop therapy have grown in popularity.

The demonstrated safety of the MIGS class is the biggest factor driving the shift toward procedural and surgical management of glaucoma. Because the current lineup of MIGS is intended for use among individuals with mild to moderate glaucoma (and in some cases, performed at the same time as cataract surgery), the extent of IOP lowering they deliver is acceptable. However, there is still unmet treatment need for patients requiring more robust IOP lowering (such as patients with moderate glaucoma and those with mild glaucoma but at high risk for progression). For these individuals, traditional MIGS may not deliver enough efficacy, whereas

filtering surgeries entail too great a risk for failure or complications to be a suitable consideration.

A novel MicroShunt device (Santen) intended for implantation via an ab externo approach during a standalone MIGS procedure offers significant potential to expand access to safe and effective procedural options for a wide assortment of patient types. Using a design that incorporates principles determined by the Poiseuille equation,¹ the device maintains a patent connection between the anterior chamber and the subconjunctival space while reducing the potential for hypotony. Further, the resulting bleb is located posteriorly, making it less susceptible to infection and conferring advantages for patients' comfort and aesthetics.

In the following articles, leading glaucoma surgeons and researchers share insights on current unmet treatment needs in glaucoma, the role and rationale of subconjunctival MIGS, and future research that will help better elucidate the utility of targeting the alternative outflow pathway.

1. Pinchuk L, Riss I, Battle JF, et al. The use of poly(styrene-block-isobutylene-block-styrene) as a microshunt to treat glaucoma. *Regen Biomater*. 2016;3(2):137-142.

ADDRESSING REMAINING UNMET NEEDS IN GLAUCOMA MANAGEMENT



Achieving subconjunctival drainage with a novel MIGS device could bridge existing gaps in treatment across a range of glaucoma severity.

BY JOSEPH F. PANARELLI, MD

Glaucoma management is continuing to evolve as more treatment modalities are made available to us. Surgical and device-based interventions with favorable safety profiles, coupled with improved ability to identify patients at an earlier timepoint in their disease, are changing the thinking around optimal first-line treatment. Most prominently, the idea of initiating treatment with topical medications is not necessarily a given.

In addition, well-recognized issues with patients' adherence with drop therapy is prompting earlier use of device and surgical options that mitigate cost concerns around complicated daily regimens and the potential for unwanted side effects. Although medications certainly have a role in management, the opportunities to reduce or eliminate the need for topical therapy are expanding.

Yet, while surgery and devices have unquestionably been beneficial for

slowing and preventing glaucomatous progression for many patients, there is still unmet need in the treatment paradigm. To the benefit of our patients, most of the remaining questions pertain to refining the approach to patient selection and figuring out when and how to use the various treatment options. Results from clinical trials and treatment guidelines inform the approach, but decisions are typically made on a case-by-case basis.

Still a Large Gap between MIGS and Traditional Surgery

Canal-based procedures

- Modest efficacy
- Superior safety profile

Traditional glaucoma surgery

- Significant IOP reduction
- Significant risk

IOP, intraocular pressure; MIGS, minimally invasive glaucoma surgery

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Figure 1. Subconjunctival MIGS help close the gap between canal-based procedures and traditional glaucoma surgery.

In truth, there has always been a need to individualize the approach to treatment based on the needs of each patient: the glaucoma evaluation is predicated on building a risk profile based on the clinical examination, testing, imaging, and patient interview; determining an individualized target pressure; and then working with the patient to decide what approach will help safely achieve the desired IOP while considering impact on quality of life. The availability of new treatment options, such as the MicroShunt (Santen), has only helped to increase the likelihood of matching the right intervention to each patient. At the same time, there may still be a need for additional options that help bridge existing gaps (Figure 1).

RETHINKING MAXIMUM MEDICAL THERAPY

The big question faced by glaucoma specialists and their patients is in figuring out where and how the various interventions fit in terms of first-, second-, and later-line treatment. Indeed, several lines of evidence suggest that individualizing decision-making to every extent possible improves the ability to achieve the ultimate goal of treatment: preventing functional blindness.

The first piece to consider is the nuance involved in determining target

IOP. A full exploration of this topic is beyond the scope of this article. Nevertheless, there is considerable confusion over whether clinicians should be guided by landmark studies, whether numerical or percentile reduction in IOP is most important, and whether and how any number of clinical factors or imaging results should be used in determining target IOP. New information has also emerged on the subject of IOP fluctuation, which can be understood in several different ways, including diurnal fluctuation, intervisit variability, and short- versus long-term fluctuation. It is more than likely that all these various types of fluctuation are clinically relevant in terms of the risk for glaucomatous progression, yet without good ways to measure fluctuation, it is also uncertain how much weight the concept should be given when establishing an IOP target.

A second issue to consider overlaps with the questions around target IOP: the growing appreciation for the benefit of early intervention. Although the relationship between IOP fluctuation in its many forms and risk of progression is far from established, it is entirely reasonable that avoiding it altogether is probably better for the final outcome. More to the point, getting to the target IOP, and better yet, stabilizing the glaucoma

while it is still early in its natural history, provides a better chance of slowing or stopping progression.

Even if glaucoma is recognized early and a decision is made to start an intervention, the next natural questions are what option will be most likely to achieve the goal of treatment and how sustainable will it be for the long term? The recently completed LiGHT trial helped to answer many questions about the role of selective laser trabeculoplasty (SLT), with the results suggesting that it should at least be offered in first-line settings.¹ Fundamentally, the suggestion underlying the earlier introduction of SLT is to remove obstacles inherent to compliance and adherence—notably, LiGHT investigators noted that at 36 months, 74.2% of patients in the SLT group were able to maintain target IOP without drops. Yet, SLT is not universally effective, and although it is repeatable, there is often a need to continue or add medication use, which reintroduces concerns about adherence.

Historically, medication was the preferred option for early treatment phases, with decisions about advancing therapy based on the clinical circumstance. It used to be fairly common to have patients on three to four different classes of medication before moving to trabeculectomy or tube shunt surgery. With the introduction of surgical options, in particular the category of MIGS devices, there has been a rethink in what constitutes maximum medical therapy (MMT). Because of the favorable safety profile associated with MIGS, there is rationale to consider them when patients are on one to two medications—with the idea that going to surgery sooner might have the added benefit of reducing or eliminating the number of required medications. In other words, it may be the case that defining MMT numerically is insufficient, and again, an individualized approach to the question may be prudent. For instance, some patients may not want to

use drops, there may be concerns about cost, side effects could be an issue, or adherence may be poor. But with the advent of MIGS, we no longer have to manage around these issues to help patients from going blind.

CONSIDERATIONS FOR SURGICAL MANAGEMENT OF GLAUCOMA

Conceptually, surgical management of glaucoma addresses many of the issues still apparent in the treatment paradigm. As a category, surgical options largely remove the requirement for patients' adherence. Although some of the MIGS options are only indicated for use at the time of cataract surgery, they still facilitate a greater ability to intervene more aggressively than medical therapy early in the disease course while maintaining safety. As a result, there is a better chance of getting patients to the target IOP sooner in the natural history. Altogether, the surgical management of glaucoma also obviates many of the questions around IOP fluctuation and its potential to contribute to progression.

Yet, not all surgical interventions are equal, and it is still imperative to balance safety and efficacy when deciding if a procedure will be of benefit. Traditionally, surgery benefits those patients above the target IOP on MMT, those who are progressing at the target IOP on MMT, or those who are not adherent to MMT. However, while such considerations speak to who is indicated, there is still a matter of what procedure—and there is still a gap between canal-based procedures that offer modest efficacy with superior safety and traditional glaucoma surgeries that offer more robust IOP reduction, but which are associated with significant risk.

The term “subconjunctival MIGS” has recently been coined to describe a less invasive approach to bleb formation (Figure 2). The goal is to safely and easily create a filtering bleb by shunting fluid

Image courtesy of Dr. Panarelli and Paul Sidoti, MD.

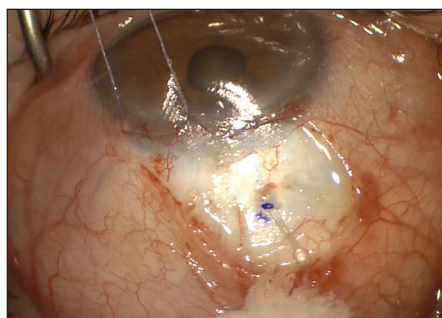


Figure 2. A novel MIGS device placed by an ab externo approach achieves bleb-based drainage from the anterior chamber to the subconjunctival space.

from the anterior chamber to the subconjunctival/sub-Tenon space in a regulated manner. The length and luminal diameter of these new microshunts help restrict flow and minimize hypotony while still allowing for the formation of diffuse, posteriorly directed blebs.

BRINGING IT ALL TOGETHER

In my practice, I weigh several factors in deciding what surgical option is appropriate for a given patient, including the type and severity of glaucoma, medication burden, health of the ocular surface, age of the patient, and how the surgery might positively or negatively impact quality of life. Of these, the latter two really speak to the art of medicine. Because we are diagnosing glaucoma at an earlier time point, and because patients are living longer and are having more active lives, we will inevitably be treating glaucoma for longer periods of time. At the same time, glaucoma itself can be devastating for patients to live with, and so there is a greater emphasis on using the appropriate tools to treat the disease when it is early and before it is progressing. To this last point, we do not want the treatment to exact any additional burden on patients' daily living.

Within this framework, the idea of using bleb-based subconjunctival MIGS via an ab externo approach early in

the natural history makes sense for a number of reasons. First, it is a reasonable option across a wide spectrum of diseases. A patient with moderate glaucoma for whom trabeculectomy is not yet indicated is a clear-cut example, but what about the young patient with mild glaucoma and a strong family history of blindness? Second, there is great potential to not just reduce but eliminate medication burden. Third, because bleb-based subconjunctival MIGS offers more potent IOP-lowering efficacy than other MIGS procedures, it has a greater chance of not just slowing but stopping progression. Fourth, the learning curve is not as arduous as some might expect. In my hands, the techniques and steps were fairly straightforward to learn and adopt.

One final compelling reason to consider earlier use of subconjunctival MIGS is the potential impact on patients' quality of life. The procedure is associated with minimal risk to affect visual acuity or cause discomfort and minimal need for postoperative management or continued intervention. It can reduce the need for drops after surgery and has little to no impact on physical appearance. Above and beyond these procedural aspects, though, it provides an opportunity to help patients achieve target pressure earlier in their disease course, so they have a better chance of avoiding any compromise to their visual ability. ■

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SUBCONJUNCTIVAL MIGS AND THE EVOLUTION OF BLEB-BASED GLAUCOMA SURGERY



A novel glaucoma device attempts to combine the robust IOP-lowering efficacy of bleb-based glaucoma surgery with the safety profile associated with the category of MIGS.

BY SYRIL DORAIRAJ, MBBS, MD, FACS

First introduced in the 1960s, trabeculectomy is a common type of glaucoma filtration surgery, indicated most often for patients with moderate to advanced disease, if there has been rapid progression, if prior medical management/laser/surgery has been unsuccessful, or if there is significant risk of future progression likely to yield loss of visual ability. During the surgery, a partial thickness scleral flap is created over a fistula to facilitate flow of aqueous into the subconjunctival space, thereby resulting in the creation of a filtering bleb under the conjunctiva (Figure). This mechanism results in IOP reduction that is often more profound than what is achievable with non-filtering surgeries or medical therapy. The extent of IOP reduction following trabeculectomy is variable and depends on several factors. Generally speaking, around 80% of patients achieve an IOP of 18 mm Hg or better and a 20% reduction following trabeculectomy with mitomycin C after 1 year of follow-up.¹

However, trabeculectomy is also associated with a not insignificant rate of failure^{2,3} and early and late complications.^{4,5} Previously, in the absence of viable alternative options for patients with more severe disease, the best way surgeons could manage risks and benefits was

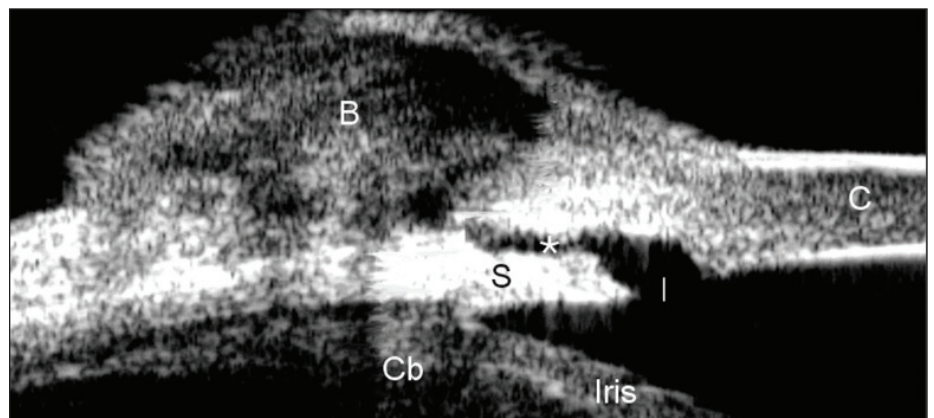


Figure. Ultrasound biomicroscopy showing a fully formed drainage bleb following trabeculectomy.

to forestall use of trabeculectomy until absolutely necessary. Even when trabeculectomy is indicated, the surgeon has to be prepared to recognize any indication of surgical failure, and intervene quickly (ie, prescribe corticosteroids, perform a secondary procedure with filtering at the inferior limbus or use of an implant, or else revise the first filter surgery). Management of failure and complications requires a much more involved approach.

The advent of MIGS, with modest IOP-lowering efficacy but favorable safety, has helped to drive a paradigm shift in the early treatment of glaucoma. A novel microtube device placed in a MIGS procedure that affects subconjunctival

drainage that is currently under investigation (MicroShunt, Santen) has the potential to help address this important unmet need in glaucoma management.

TRABECULECTOMY COMPLICATIONS

Trabeculectomy is most often considered when the potential benefit outweighs the risk, which can be understood as either the potential for the surgery to fail or for the patient to develop complications in the postoperative period. Paradoxically, even though there would seem to be a benefit to waiting as long as possible to intervene surgically (ie, only when absolutely necessary), glaucoma surgery has been identified as a risk factor for progressive

visual field loss.⁶ Thus, it is advantageous to intervene in the earlier stages of the disease, although the options to do so are somewhat limited after the patient has progressed past mild disease. In this regard, it would be advantageous to identify patients at risk for rapid progression on their visual field, who in turn might require more aggressive management. Some risk factors have been identified, including older age, higher peak IOP, pseudoexfoliative glaucoma, and worse baseline mean deviation on visual field.⁶ In the latter study, previous glaucoma surgery was also identified as a risk factor, although the retrospective nature of the analysis limits a full understanding of this finding. It would be interesting to understand risk for rapid progression according to type of surgery and glaucoma severity; it is plausible that trabeculectomy and other filtering surgeries might infer greater risk for rapid progression compared to MIGS. More data are needed to improve patient selection for rapid progressors.

The list of known risk factors for trabeculectomy failure is more of a known commodity, including African descent, younger age, previous surgery on the conjunctiva, neovascular glaucoma, uveitis, and a history of topical medication use.⁷ In some respects, the surgery itself is a risk factor. The act of incising the conjunctiva instigates activity in the epithelial and mesenchymal cells that promote cellular proliferation, migration, and tissue remodeling.⁸ Likewise, tissue injury activates a number of biological processes that ultimately induce the release of a variety of proinflammatory and profibrogenic mediators, such as activation of neutrophils and macrophages that release proinflammatory cytokines and chemo-

kines (eg transforming growth factor beta [TGF- β]), and upregulated fibroblast differentiation into myofibroblasts that secrete contractile proteins and reduce tissue functionality. Angiogenesis after trabeculectomy leads to wound healing and fibrosis.

A variety of measures have been offered to reduce the potential for surgical failure and postoperative complications. Once patients are carefully selected for trabeculectomy, there is a need to cycle them off medications preoperatively that may contribute to inflammation (such as brimonidine and prostaglandins) and to start a course of oral or topical steroids. There are a number of steps the surgeon can take intraoperatively, including avoiding conjunctival buttonholes and tears, avoiding over cauterizing, and scraping episcleral tissue to prevent overgrowth. Careful monitoring in the early postoperative phase is recommended to identify whether the bleb is functional—and if it is not, options such as digital massage, removal of a suture, or use of antimetabolites (5-fluorouracil) may be employed. Over time, monitoring is continued, perhaps in conjunction with anterior chamber OCT. In cases of filtration failure, particularly in the late phases, bleb needling is a consideration. Fundamentally, what all of these measures speak to is a need for the surgeon to maintain an active role after the surgery is complete, to recognize early signs of trouble, and to act quickly to avoid unwanted outcomes.

A DIFFERENT KIND OF BLEB-BASED PROCEDURE

Based on our collective experience and published literature, it is safe to say that no

other option is as effective as bleb-based surgeries in lowering IOP. However, not all bleb-based surgeries are equal in terms of the safety profile. In the Tube Versus Trabeculectomy (TVT) study, early complications occurred at greater frequency in the trabeculectomy group, and the rate of late complications was also higher, compared to the tube group.⁹ Specifically, wound leak, dysethesia, and bleb leak were each found to occur significantly more frequently in the trabeculectomy group compared to tube, whereas no early or late complications occurred at greater frequency in the tube group compared to trabeculectomy.⁹ Of additional note, incidence of hypotony maculopathy, and endophthalmitis/blebitis were all higher in the trabeculectomy group.⁹ ■

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BALANCING SAFETY AND EFFICACY: EXPANDING ON CURRENT MIGS OFFERINGS



Subconjunctival MIGS could be an option for using bleb-based surgery earlier in the treatment paradigm.

BY ALEX S. HUANG, MD, PHD

Balancing safety and efficacy has long been an important concept in glaucoma surgery. Some of the earliest procedural interventions used in glaucoma, including goniotomy and trabeculotomy, emphasized being minimally traumatic to the eye. However, IOP-lowering efficacy was the limitation. On the other end of the spectrum are traditional bleb-based surgeries—trabeculectomy and tubes—that offer more robust IOP lowering but which are associated with greater risk, including wound leaks, suprachoroidal hemorrhage, hypotony, cystoid macular edema, shallow or flat anterior chamber, and aqueous misdirection during the perioperative period,¹ along with risk of hypotony, blebitis, and endophthalmitis during long-term follow-up.² The fact that these kinds of invasive surgeries still have a role is a tacit acknowledgement that some cases of glaucoma—those associated with more rapid or a higher risk of progression and thus a greater threat to visual ability—require an aggressive approach with a necessary tradeoff in terms of risk.

The most recent era in the evolution of glaucoma surgery, the introduction of MIGS, is a return to the idea of going small, thereby prioritizing safety. Because they are indicated for earlier stage glaucoma, they tend to achieve suitable IOP lowering, help stabilize the disease, and thus, lower risk of progression. Additional

benefits, including reducing medication requirement, may be realized. For their intended purpose, then, MIGS elegantly deliver a balance of safety and efficacy. At the same time, the current catalogue of MIGS options may not sufficiently address the spectrum of glaucoma presentations seen in clinical practice, such as in advanced disease. There is a need for new options that offer slightly more in terms of efficacy without sacrificing the safety associated with this class.

ENHANCING IOP LOWERING WITH MIGS

MIGS devices are generally associated with a favorable safety profile; a systematic review and meta-analysis by Lavia et al found that IOP spikes were the most frequently reported complications but infection and BCVA loss due to glaucoma has not been reported.³ While there needs to be more data comparing MIGS surgery with medical therapy or other MIGS devices, the weight of available evidence provides confidence in recommending MIGS devices for a wide assortment of patient types across a spectrum of glaucoma presentations. While individual results are always variable, outcomes with MIGS devices that target conventional drainage pathways are fairly predictable, with IOP among responders resolving to the mid-teens. However, in thinking about the entire aqueous drainage process, IOP after

trabecular meshwork bypass results in a pressure gradient relative to the episcleral venous pressure, which has an average pressure of around 8 mm Hg.⁴

Thus, while the current MIGS class is largely successful for mild to moderate glaucoma, the potential to achieve even lower IOPs without unduly affecting safety represents an unmet need. To achieve this, there are a number of potential strategies. First, one could consider combining MIGS and medications. In our lab, we have seen evidence that nitric oxide derivatives can dilate distal collector channels, thereby helping to restore physiologic aqueous drainage (unpublished data). Rho-kinase inhibitors have been shown by others to lower episcleral venous pressure.⁴ Thus, addition of medical therapy targeting distal outflow might synergize with the IOP-lowering efficacy of procedural approaches.

MIGS + BLEBS

Another approach to achieving greater IOP lowering in a minimally invasive manner is to combine a filtering bleb to a MIGS procedure, also known as *MIGS + Blebs*. Combining safety and efficacy, this can create an important option across a wide range of glaucoma severity (Figure). This also explains the rationale behind the MicroShunt device (Santen). For MIGS type safety, the MicroShunt is 8.5 mm in length, with an outer diameter of 350 μ m and an internal lumen of 70 μ m. The lumen diameter provides



Image modified and reproduced with permission from Weinreb RN, et al. *Am J Ophthalmol*. 2004.

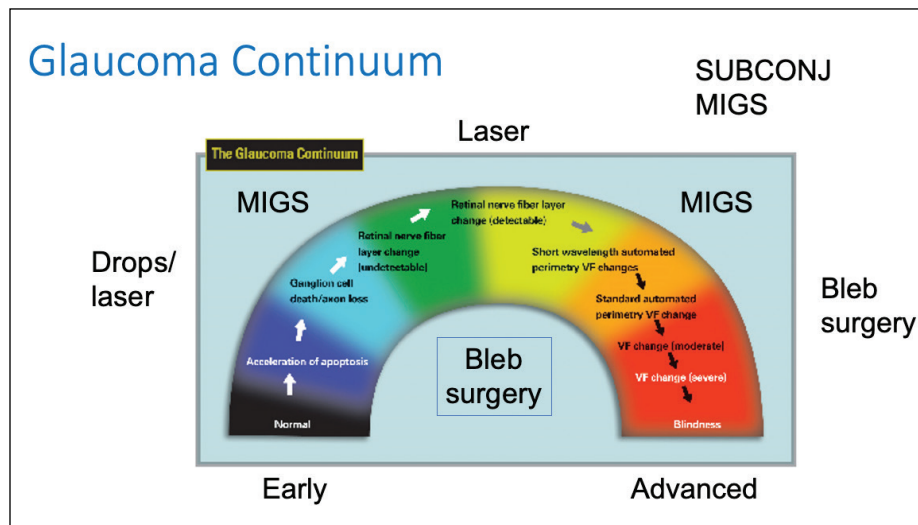


Figure. Subconjunctival MIGS is conceivably broadly applicable across a spectrum of glaucoma severity, offering more robust IOP-lowering efficacy compared to other MIGS surgeries but while maintaining the safety associated with the class.

just enough flow resistance to minimize hypotony. Further, resultant blebs from MIGS + Blebs are located posteriorly, which can make them less susceptible to infection and achieve better comfort and aesthetic. Together, these considerations can greatly reduce risk.

For efficacy, bleb-based surgeries fundamentally need to accomplish three things: (1) create a connection between the anterior chamber and the subconjunctival space but without (2) resulting in scarring of the conjunctiva. Lastly, (3) the bleb must serve as a reservoir that continually drains with an exit path. By the introduction of a device, such as the MicroShunt, the first criteria is met via a minimally invasive and permanent fashion while avoiding the need to make scleral flaps.

The second criteria must also be considered, and tremendous work has

already been performed with the advent of antimetabolites that reduce scarring. Antimetabolites will still be necessary in MIGS + Blebs. Future work is being done to innovate more specific agents than what we have now.

Lastly, for fluid drainage, there has been longstanding controversy about how aqueous leaves a bleb. Currently, the best evidence suggests that the aqueous that accumulates within a formed bleb is drained to the rest of the body via conjunctival lymphatic vessels. Of note, my research lab is actively involved in a number of studies to answer this question, and we anticipate publishing our data soon. For now, we can say that we have what we believe to be confirmatory evidence that lymphatic drainage plays a functional role in bleb drainage at least in most cases, and that we are doing

additional research to determine whether lymphatic drainage is a necessary component of successful bleb drainage.

Taken together, by combining MIGS + Blebs the hope is to draw upon our MIGS lessons and safety profile and combine that with greater IOP reduction achieved using blebs. By further studying and better understanding subconjunctival MIGS and subconjunctival outflow, we can continue to balance safety and efficacy. ■

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