Eye (2010) 24, 441–449

www.nature.com/eye

CAMBRIDGE OPHTHALMOLOGICAL SYMPOSIUM

Surgical management of the late complications of proliferative diabetic retinopathy

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Abstract

The late complications of proliferative diabetic retinopathy (PDR) comprise vitreous haemorrhage, tractional retinal detachment, combined tractional–rhegmatogenous retinal detachment, and severe fibrovascular proliferation (including macular distortion or dragging, tractional macular oedema, and media opacity due to fibrovascular tissue). This article will review the indications, techniques, and outcomes of vitrectomy surgery to treat these conditions. A careful assessment of the surgical anatomy, with particular attention to the configuration of vitreoretinal attachments, is important when determining the precise surgical procedure required. The surgical outcome after diabetic vitrectomy has steadily improved with advances in vitreoretinal surgical instrumentation and technique. Significant post-operative complications may, however, occur including cataract formation, recurrent vitreous cavity haemorrhage (early or delayed), rhegmatogenous retinal detachment, and neovascular glaucoma. Most patients will regain or retain useful vision after diabetic vitrectomy, although the visual outcome does remain unpredictable. The development of adjunctive pharmacotherapy should enable further improvements in visual outcome in the future.
Eye (2010) **24,** 441–449; doi:10.1038/eye.2009.325; published online 5 February 2010

Keywords: diabetic retinopathy; vitrectomy; vitreous haemorrhage; retinal detachment; retinal neovascularisation; macular oedema

Introduction

The late complications of proliferative diabetic retinopathy (PDR) comprise vitreous haemorrhage, tractional retinal detachment, combined tractional–rhegmatogenous retinal detachment, and severe fibrovascular proliferation (including macular distortion or dragging, tractional macular oedema, and media opacity due to fibrovascular tissue). These vitreoretinal conditions have been treated with increasingly successful outcomes since the introduction of pars plana vitrectomy in the early 1970s.[1] This article will review the concepts and techniques which underpin the current surgical management of the late complications of PDR.

Pathophysiology and surgical anatomy

The initial insult in the development of PDR is considered to be retinal ischaemia leading to the production of angiogenic factors.[2] The process of retinal neovascularisation probably results from a complex interaction between several angiogenic factors with vascular endothelial growth factor (VEGF) having a prominent role. These new vessels proliferate in the vitreoretinal interface, accompanied by varying degrees of fibrous tissue proliferation, leading to the development of fibrovascular membranes. The fibrovascular membranes are usually asymptomatic at this stage, although small haemorrhages can sometimes occur near the growing ends of new vessels.

The late complications of PDR subsequently result from the development of posterior vitreous detachment and/or contraction of these fibrovascular membranes.[3] The process of posterior vitreous detachment in eyes with PDR is altered by the presence of fibrovascular membranes, leading to the development of tractional forces at the sites of vitreoretinal attachment. These tractional forces can lead to various outcomes: vitreous haemorrhage, tractional retinal detachment, and combined

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Received: 2 November 2009
Accepted: 17 November 2009
Published online: 5 February 2010

This paper was presented at the Cambridge Ophthalmological Symposium in September 2009.

tractional–rhegmatogenous retinal detachment (retinal break formation usually occurs near fibrovascular epicentres) (Figure 1). Alternatively, contraction of a fibrovascular membrane sheet across the posterior pole can lead to macular distortion or dragging. It should be recognised that some tractional elevations of the retina in PDR are tractional retinoschisis rather than tractional retinal detachment.[4,5]

Surgical management of the late complications of PDR is strongly influenced by the extent of posterior vitreous separation and the location and type of any vitreoretinal attachments.[3] A minority of patients have a complete posterior vitreous separation without any residual vitreoretinal attachments (though epiretinal membranes may still be present). Most patients, however, have a partial vitreous separation with varying degrees of residual vitreoretinal attachment predominantly located at the posterior pole. There are two basic types of vitreoretinal attachment, focal and broad, which develop from the fibrovascular epicentres. Focal vitreoretinal attachments are point-like attachments, which may be single or multiple with variable degrees of intervening posterior vitreous separation. Broad vitreoretinal attachments present as a fibrovascular plaque with two configurations: (1) those without underlying retinal folds which develop from a large segment of retinal neovascularisation and (2) those with underlying retinal folds which develop from coalescence and contraction of multiple focal fibrovascular epicentres.

Surgical indications

The Diabetic Retinopathy Vitrectomy Study (DRVS) defined the benefit of early vitrectomy in the management of severe vitreous haemorrhage. This study evaluated patients with severe vitreous haemorrhage that reduced visual acuity to 5/200 or less for at least 1 month who were randomised to early vitrectomy or deferral of vitrectomy for 1 year. Patients in the deferral group underwent vitrectomy if persistent vitreous haemorrhage was present after 12 months, or sooner if retinal detachment involving the centre of the macula was detected by ophthalmoscopic or ultrasonographic examination at any time during follow-up. This study demonstrated that a final visual acuity of 20/40 or better at 2 years follow-up was achieved by 25% of the early vitrectomy group and 15% of the deferral group ($P = 0.01$).[6] The greatest benefit was demonstrated for patients with type 1 diabetes who tended to have more severe PDR. The benefits of early vitrectomy remained after 4 years follow-up.[7]

The DRVS study also defined the benefit of early vitrectomy in the management of severe active fibrovascular proliferation. In this study, patients with

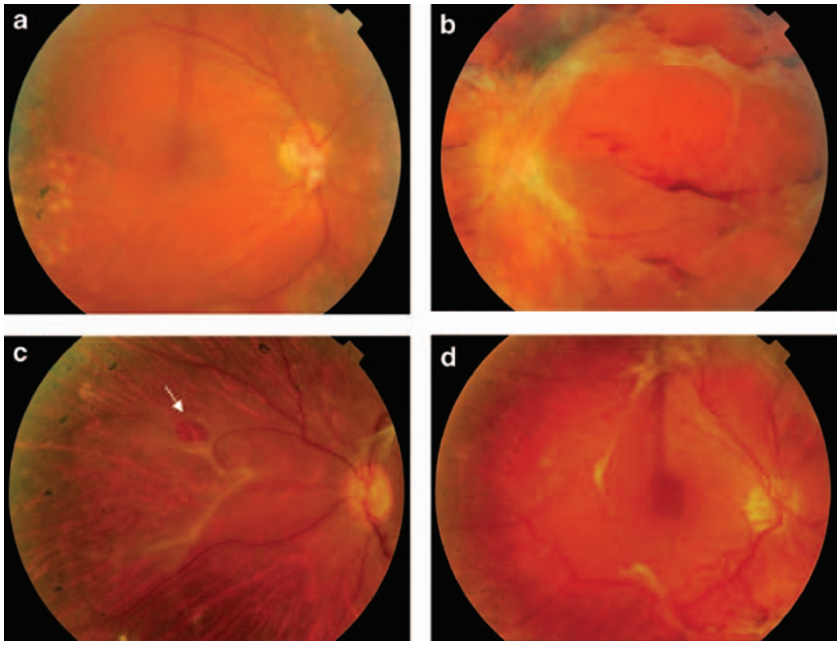

Figure 1 (a) Mild vitreous haemorrhage due to fibrovascular membrane at the optic disc with a focal vitreoretinal attachment. (b) Tractional retinal detachment involving the macula due to extensive fibrovascular membranes along the vascular arcades with multiple broad vitreoretinal attachments. (c) Combined tractional–rhegmatogenous retinal detachment nasal to the optic disc with multiple focal vitreoretinal attachments. Note location of the retinal break adjacent to a fibrovascular epicentre. (d) Macular distortion due to contraction of a fibrovascular membrane sheet across the posterior pole.

severe active fibrovascular proliferation who had useful vision (visual acuity of 10/200 or better) were randomised to early vitrectomy or conventional management (observation, photocoagulation, or vitrectomy for complications such as retinal detachment involving the centre of the macula and severe vitreous haemorrhage persisting for 6 months or more). This study demonstrated that a final visual acuity of 20/40 or better at 4 years follow-up was achieved by 44% of the early vitrectomy group and 28% of the conventional management group ($P<0.05$).[8] The greatest benefit was demonstrated in eyes with the most severe fibrovascular proliferation.[8,9] The proportion of patients with very poor visual outcome was similar in the two groups. It is important to note that the DRVS study was conducted without panretinal photocoagulation being performed during surgery.

The indications for surgical management of the late complications of PDR have steadily evolved since the DRVS reports. Persistent or recurrent vitreous haemorrhage remains a common indication for surgery with flexible criteria generally being applied now regarding the decision and timing of vitrectomy surgery. Various factors should be considered including the degree of visual impairment (with consideration of the visual status of the fellow eye), predicted time course for spontaneous resolution, predicted risk of developing further vitreous haemorrhages, adequacy of previous laser treatment to control retinal ischaemia, presence of underlying tractional retinal detachment involving or threatening the macula, and presence of untreated diabetic maculopathy. It is particularly important not to underestimate the impact of unpredictable visual impairment experienced by patients with frequent recurrent vitreous haemorrhages.

Tractional retinal detachment with recent macular involvement is a well-established indication for vitrectomy surgery, although the visual outcome may be variable due to irreversible macular dysfunction.[10–14] The surgical indications have gradually been expanded over time with increasing clinical experience to include 'macular threatening' tractional retinal detachments. It is important, however, to note that extramacular tractional retinal detachments can generally be safely observed as they tend to remain stable over prolonged periods of time.[15] The presence of a combined tractional–rhegmatogenous retinal detachment necessitates closer monitoring, regardless of macular status, because there is a significant risk of progression requiring vitrectomy surgery.[16,17]

Severe fibrovascular proliferation is a less common indication for vitrectomy surgery comprising macular distortion or dragging, tractional macular oedema, and media opacity due to fibrovascular tissue. The indications for vitrectomy surgery for this group of patients have also steadily evolved with increasing clinical experience since the era of the DRVS study.[8,9] Some additional indications for vitrectomy surgery include dense premacular subhyaloid haemorrhage, ghost cell/haemolytic glaucoma uncontrolled by medical treatment, and anterior segment neovascularisation with media opacity.[3] There may also be a role for vitrectomy surgery in the treatment of diabetic macular oedema with vitreomacular traction.[18]

Surgical procedure

The surgical objectives of a diabetic vitrectomy comprise: (1) removal of vitreous opacities, (2) dissection and excision of fibrovascular membranes with elimination of vitreoretinal traction, (3) retinal reattachment using intraocular tamponade, if necessary, and (4) prevention of reproliferative neovascularisation by laser photocoagulation. The precise surgical procedure required is highly variable because it is dependent upon the surgical anatomy presented by each individual case. In addition, a patient's general medical status requires consideration when planning vitrectomy surgery (including control of risk factors for diabetic retinopathy progression).

The complexity of a diabetic vitrectomy is largely determined by the configuration of the vitreoretinal attachments.[3] Minor complexity procedures comprise cases with vitreous haemorrhage and a complete posterior vitreous detachment, in which no fibrovascular membrane dissection is required. Medium complexity procedures comprise cases with focal vitreoretinal attachments (single or multiple) or broad vitreoretinal attachments without underlying retinal folds, in which there are multiple small neovascular pegs. Major complexity procedures generally comprise cases with broad vitreoretinal attachments with underlying retinal folds, in which the surgical plane is less clearly defined because of diffuse fibrovascular membrane attachment.

A variety of surgical techniques has been developed for dissection of diabetic fibrovascular membranes which broadly comprise segmentation, delamination, and en bloc delamination.[3] The en bloc delamination technique involves removal of the fibrovascular membranes and posterior hyaloid from the retina as a single unit.[14] This technique facilitates the dissection process by maintaining anterior-posterior traction which fixates the fibrovascular membranes. It is also mportant to recognise the presence of vitreoschisis when identifying the correct surgical plane for delamination.[19] A flexible approach is often required during vitrectomy surgery because several dissection techniques may be required in a single case. The creation of iatrogenic

retinal breaks can, in particular, convert a 'simple' case into a much more complex procedure.

Vitreoretinal surgical instrumentation and technique has steadily evolved since the introduction of pars plana vitrectomy. Recent advances have included non-contact wide-angle viewing systems and fibreoptic Xenon illumination systems which have greatly improved vitreoretinal visualisation.[20] A wide variety of vitreoretinal instrumentation is now available for diabetic vitrectomies comprising scissors, forceps, cannulas, endodiathermy instruments, and endolaser probes (including various multifunction instruments). Currently, there is considerable interest in using transconjunctival sutureless vitrectomy systems (23G or 25G) which offer potential advantages of reduced operative time and more rapid post-operative recovery. However, these smaller gauge vitrectomy systems still have some significant limitations for more complex diabetic vitrectomies.[21]

The introduction of phaco-vitrectomy procedures (combined phacoemulsification cataract surgery with pars plana vitrectomy) is another recent development.[22] A combined procedure is clearly beneficial in patients with significant cataract limiting per-operative vitreoretinal visualisation. However, it is important to be cautious regarding combined procedures in patients with severe PDR because they may develop significant anterior segment complications.[23] Furthermore, the incidence of cataract formation is lower after diabetic vitrectomy than other vitrectomy procedures, particularly in younger patients.[24] It is therefore generally preferable to defer phacoemulsification cataract surgery until a visually significant cataract has developed after diabetic vitrectomy (with appropriate recognition of the potential complexity of post-vitrectomy cataract surgery).[25]

Complications after diabetic vitrectomy

A wide variety of complications can occur after diabetic vitrectomy. The most common complications comprise corneal epithelial defects, elevated intraocular pressure, cataract formation, recurrent vitreous cavity haemorrhage (early or delayed), rhegmatogenous retinal detachment, and neovascular glaucoma.[3,26] The development of complications can be minimised by meticulous surgical technique and careful post-operative follow-up. Corneal epithelial defects have become much less common following the introduction of non-contact wide-angle viewing systems.[27] Elevated intraocular pressure is a common complication, due to trabecular meshwork obstruction by erythrocytes and/or the effects of intraocular gas tamponade, which can usually be readily controlled by medical treatment.[28] Prophylactic ocular hypotensive medication may be helpful in preventing this complication.

Early vitreous cavity haemorrhage (within 1 week of surgery) is a common complication after diabetic vitrectomy, affecting 30–75% of patients.[3] The main causes are bleeding from dissected fibrovascular tissue and dispersion of erythrocytes from residual peripheral vitreous gel. Various preventive strategies have been proposed to reduce the incidence of this complication. Careful dissection of fibrovascular membranes with complete haemostasis (by diathermy or direct pressure) is clearly an important factor. Intraocular tamponade with air or gas can be considered for post-operative haemostasis, although variable findings have been reported.[29–31] Peri-operative administration of intravenous tranexamic acid (an antifibrinolytic agent) does not provide any benefit.[32,33] More recently, intravitreal anti-VEGF therapy with bevacizumab administered 1–2 weeks pre-operatively has been reported to provide some benefit.[34–36] Early vitreous cavity haemorrhages usually clear spontaneously within 2–6 weeks without requiring further intervention.

Delayed vitreous cavity haemorrhage (occurring 3 months or greater after surgery) affects around 10–20% of patients.[3] The main causes are residual fibrovascular membranes, reproliferative retinal neovascularisation, and sclerotomy entry site neovascularisation (fibrovascular ingrowth).[37,38] An important preventive strategy is laser photocoagulation to eliminate any post-operative neovascular stimulus if existing panretinal photocoagulation is inadequate (including treatment of the peripheral retina).[39] Cryotherapy to the peripheral retina and sclerotomy entry sites has also been advocated.[38] Delayed vitreous cavity haemorrhages are a significant problem for some patients which may fail to clear spontaneously requiring further vitrectomy surgery. Treatment comprises vitreous cavity washout, dissection of residual or reproliferative fibrovascular membranes, additional laser photocoagulation (including treatment of the peripheral retina), and cryotherapy to the sclerotomy entry sites.[37] Silicone oil tamponade may occasionally be required to maintain clear media.

Severe complications after diabetic vitrectomy include rhegmatogenous retinal detachment, neovascular glaucoma, and anterior hyaloidal fibrovascular proliferation. Rhegmatogenous retinal detachment (incidence around 5%) is a serious complication resulting from peripheral or, less commonly, posterior retinal breaks which can rapidly lead to proliferative vitreoretinopathy and/or anterior segment neovascularisation.[26,40] It is important that every diabetic vitrectomy includes a careful peripheral retinal examination in order to identify and treat any peripheral retinal breaks.[20] Rhegmatogenous retinal detachments

can usually be treated by further vitrectomy surgery, although the visual outcome is often poor.[26,40] Neovascular glaucoma (incidence around 3%) is generally restricted to cases with severe retinal ischaemia and inadequate laser photocoagulation.[26] Treatment comprises urgent panretinal photocoagulation with consideration of adjunctive intravitreal anti-VEGF therapy.[41] Anterior hyaloidal fibrovascular proliferation is a rare complication comprising anterior extraretinal neovascularisation which can lead to tractional detachment of the peripheral retina or ciliary body.[42]

Surgical outcome

The DRVS study was a randomised clinical trial which established the benefit of early vitrectomy in the management of the late complication of PDR. For patients with severe vitreous haemorrhage, a good visual outcome (20/40 or better) was achieved in 25% of patients and a poor visual outcome (worse than 5/200) occurred in 36% of patients at 2 years follow-up.[6] This visual outcome profile was maintained after 4 years follow-up.[7] For patients with severe active fibrovascular proliferation, a good visual outcome (20/40 or better) was achieved in 44% of patients and a poor visual outcome (worse than 5/200) occurred in 28% of patients at 4 years follow-up.[8] The DRVS study reported a visual outcome of no light perception in around 25% of patients overall.[6–8] It is important, however, to note that panretinal photocoagulation was not performed during vitrectomy surgery in the DRVS study.

Vitrectomy surgery for tractional retinal detachment or combined tractional–rhegmatogenous retinal detachment has not been assessed in a randomised clinical trial. The surgical outcome for these conditions was, however, reported in several case series during the era of the DRVS study.[10–14,16,43] The specific surgical procedure of vitrectomy with en bloc delamination of fibrovascular membranes has been reported for diabetic tractional retinal detachment involving the macula.[14] This study of 69 cases reported complete retinal reattachment in 83% of cases and macular reattachment in 88% of cases with a minimum of 6 months follow-up. The visual outcome was reasonably good with 43% of cases achieving 20/100 or better and 71% of cases achieving 5/200 or better. Unfortunately, the visual outcome was often limited by irreversible macular dysfunction despite achieving retinal reattachment.

The surgical outcome after diabetic vitrectomy has steadily improved since the era of the DRVS study with advances in vitreoretinal surgical instrumentation and technique.[17,26,44–48] It is difficult to compare surgical outcomes reported in different studies due to multiple confounding factors. For a historical perspective, however, it is interesting to compare two studies which both reported unselected cohorts of patients requiring surgery for the late complications of PDR (Table 1). The first study was reported from the Wilmer Ophthalmological Institute analysing the period 1975 to 1983.[49] The second study was reported from Moorfields Eye Hospital analysing the period 2004 to 2005.[26] The surgical indications for diabetic vitrectomy were broadly comparable in these two studies. It is clear that the proportion of good visual outcomes has increased and the proportion of poor visual outcomes has reduced during this 25-year period. Currently, vision improves in around 75% of patients and worsens in around 10% of patients after diabetic vitrectomy.[26]

The predictive factors of a poor visual outcome after diabetic vitrectomy have been evaluated in many studies.[13,16,17,26,46,47,50–52] Consistent predictive factors have included poor pre-operative visual acuity, macular detachment, complex fibrovascular membrane dissection (surrogate indicators comprising iatrogenic retinal breaks and use of long-acting intraocular tamponade), and iris neovascularisation. The only readily modifiable predictive factor is complex fibrovascular membrane

Table 1 Historical comparison of surgical outcome after diabetic vitrectomy

	Wilmer Ophthalmological Institute (Baltimore, USA)[49]	*Moorfields Eye Hospital (London, UK)*[26]
Time period of study	1975–1983	2004–2005
Number of cases	1007	174
Surgical indication:		
Vitreous haemorrhage	35%	49%
Tractional RD	36%	37%
Combined TRRD	17%	12%
Other indications	12%[a]	2%[b]
Visual outcome:		
20/40 or better	17%	29%
20/100 or better	36%	59%
Worse than 5/200	30%	16%
No light perception	14%	2%
Change in visual acuity:		
Improved by $\geqslant$0.3 logMAR units	Not reported	75%
Worsened by $\geqslant$0.3 logMAR units	Not reported	9%

RD, retinal detachment; TRRD, tractional–rhegmatogenous retinal detachment.
[a]Cases comprised progressive fibrovascular proliferation (causing visual loss due to mechanisms such as vitreopapillary traction and fibrous tissue covering or distorting the macula).
[b]Cases comprised rubeosis with vitreous haemorrhage and uncontrolled new vessels.

dissection. The improvement in visual outcome achieved during the past 25 years has therefore mainly resulted from advances in vitreoretinal surgical instrumentation and technique enabling more effective dissection of complex fibrovascular membranes. The visual outcome after diabetic vitrectomy does, however, continue to remain unpredictable.[26] One significant problem is the difficulty in determining the presence of diabetic macular ischaemia before vitrectomy surgery.

Adjunctive pharmacotherapy

Adjunctive pharmacotherapy is another therapeutic strategy to improve visual outcomes after diabetic vitrectomy. This approach has previously been investigated without any significant benefit using pharmacological agents such as tissue plasminogen activator (tPA) or plasmin to induce enzymatic vitreous separation[53–55] and tranexamic acid to prevent recurrent vitreous cavity haemorrhage.[32,33] Currently, triamcinolone acetonide and anti-VEGF agents (bevacizumab, ranibizumab, and pegaptanib) are showing promise as new treatments for diabetic macular oedema and PDR.[56,57] These pharmacological agents can be administered either alone or in combination with laser photocoagulation. There is increasing evidence that combination therapy may be the optimum therapeutic strategy in selected cases of diabetic macular oedema and PDR.[56,57] Adjunctive pharmacotherapy using these agents might also lead to improvements in visual outcome after diabetic vitrectomy.

Triamcinolone acetonide (intravitreal or sub-Tenon's administration) can provide effective short-term treatment of diabetic macular oedema.[58,59] The visual outcome after diabetic vitrectomy may sometimes be limited by the presence of new or persistent diabetic macular oedema. Laser photocoagulation is currently the standard treatment for patients with post-operative diabetic macular oedema. Recently, sub-Tenon's triamcinolone acetonide has been reported as an effective treatment for refractory diabetic macular oedema after vitrectomy surgery.[60,61] It is possible that per-operative adjunctive pharmacotherapy with triamcinolone acetonide (intravitreal or sub-Tenon's administration) could improve the visual outcome after diabetic vitrectomy in selected cases by controlling post-operative diabetic macular oedema, although there is no definitive evidence to date.[62,63] It is, however, important to also consider the adverse effects of triamcinolone acetonide, which comprise elevated intraocular pressure and cataract formation.[59]

Anti-VEGF agents (such as bevacizumab) can produce rapid regression of retinal neovascularisation in PDR.[64] Adjunctive pharmacotherapy with anti-VEGF agents may therefore be beneficial in patients with severe active PDR requiring diabetic vitrectomy. Intravitreal bevacizumab administered 1–2 weeks pre-operatively has been reported to facilitate surgical dissection of fibrovascular membranes in eyes with severe active PDR.[35,36,65–67] The risk of recurrent vitreous cavity haemorrhage may also be reduced by this treatment.[34] However, there is a potential adverse effect because fibrovascular membrane contraction can lead to rapid development or progression of tractional retinal detachment.[66–68] The timing of vitrectomy surgery may therefore be critical to avoid this complication. Intravitreal bevacizumab may also be beneficial in the treatment of anterior segment neovascularisation associated with severe PDR.[41,64,69] There are currently no reports of other anti-VEGF agents (such as ranibizumab and pegaptanib) being used as adjunctive pharmacotherapy for diabetic vitrectomy. The precise role and optimum timing of adjunctive pharmacotherapy with anti-VEGF agents for diabetic vitrectomy remains to be determined.

Conclusion

Surgical management of the late complications of PDR remains a commonly performed vitreoretinal procedure. Most patients will regain or retain useful vision after diabetic vitrectomy, although the visual outcome remains unpredictable.[26] The evaluation of healthcare interventions increasingly requires an assessment of quality of life outcome measures. Diabetic vitrectomy has been demonstrated to significantly improve vision-related quality of life.[45,70] Early vitrectomy for diabetic vitreous haemorrhage has also been shown to be a highly cost-effective intervention.[71] Furthermore, it is important to recognise that a significant proportion of patients will develop late complications of PDR requiring vitrectomy surgery in their fellow eye (25–40% of patients within 4 years).[45,72] The surgical outcome after diabetic vitrectomy has continued to steadily improve with advances in vitreoretinal surgical instrumentation and technique. The development of adjunctive pharmacotherapy should enable further improvements in the future.

Conflict of interest

The author declares no conflict of interest.

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