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Review

Considerations for management of patients with diabetic macular edema: Optimizing treatment outcomes and minimizing safety concerns through interdisciplinary collaboration

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ABSTRACT

Diabetes is a growing worldwide epidemic and a leading cause of blindness in working-age people around the world. Diabetic retinopathy (DR) and diabetic macular edema (DME) are common causes of visual impairment in people with diabetes and often indicate the presence of diabetes-associated preclinical micro- and macrovascular complications. As such, patients with DR and DME often display complex, highly comorbid profiles. Several treatments are currently available for the treatment of DME, including anti-vascular endothelial growth factor (VEGF) agents, which are administered via intravitreal injection. While the safety profiles of approved ocular anti-VEGF therapies have been reassuring, the high-risk nature of the DME patient population means that treatment must be carefully considered and a holistic approach to disease management should be taken. This requires multidisciplinary, collaborative care involving all relevant specialties to ensure that patients not only receive prompt treatment for DME but also appropriate consideration is taken of any systemic comorbidities to evaluate and minimize potentially serious safety issues.

Contents

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1. Introduction

Diabetes is one of the leading causes of premature blindness in the world [1–3]. A key contributing factor to this is inadequate glycemic control [4,5]; despite the advent of multiple new agents to treat hyperglycemia, with lower risk of weight gain and hypoglycemia than previous treatments, many people with diabetes are not meeting their glycemic targets [6,7]. This increases the risk of developing serious comorbidities, such as cardiovascular disease, stroke, nephropathy, and neuropathy [2,8,9]. However, the comorbidity most feared by people with diabetes is diabetic retinopathy (DR) [10,11]. This is with good reason; not only can untreated DR progress to diabetic macular edema (DME), one of the most common causes of visual impairment in people with diabetes [12,13], but it often heralds the presence of preclinical micro- and macrovascular complications [4,14–16]. Indeed, the presence of DME is strongly predictive of cardiovascular disease and stroke [17]. Among individuals with diabetes, vision loss is one of the most feared complications [10,11]. Vision is vital for people with diabetes to retain their independence and manage their disease by being able to see well enough to prepare insulin for injection, check blood sugar levels, and take medications [18].

People with diabetes are often primarily under the care of their primary care physician and/or diabetologist [19,20]. Separately, patients may have their disease monitored at retinal photography clinics or by other specialists [20], such as nephrologists or podiatrists. The primary care physician is central in coordinating this care, and in terms of eye care, is responsible for ensuring screening checks and prompt referral to an ophthalmologist, if indicated [21]. However, a recent review by Seidu et al. concluded that, when implementing diabetes care programs, stand-alone interventions, such as primary care physician or nurse education alone, should be avoided [22]. As well as being expensive to deliver, the outcomes were found to be less effective in improving glycemic control than implementation of multifaceted professional interventions on multidisciplinary teams [22]. Continuous quality improvement programs have been essential for ensuring people with diabetes receive adequate and timely care, including the detection of previously undiagnosed comorbidities and complications [23]. Management of risk factors for DR and DME can also help to reduce the risk for other comorbidities associated with diabetes [5,24]. Furthermore, effective treatments for DME that can attenuate and even reverse progression of the disease process are now available [25–28].

2. Pathogenesis of DME

The pathogenesis of DME is multifaceted, complex and not yet fully elucidated [29]. Nevertheless, sustained hyperglycemia and subsequent damage to the microvasculature and breakdown of the blood–retina barrier are thought to be key processes in the development of the disease [29].

Chronic hyperglycemia is thought to promote DME development through oxidative damage, protein kinase C activation and the release of advanced glycation end products [29]. Downstream of these changes, vasoconstriction can lead to altered blood flow to the retina and hypoxia [29]. As a compensatory mechanism, expression of vascular endothelial growth factor (VEGF) is upregulated, contributing to disruption of the blood–retinal barrier by increasing vascular permeability [29]. An accumulation of fluid within the layers of the macular (macular edema) subsequently results from the increased, abnormal flow of fluid into the neurosensory retina [29].

3. Clinical features of DME

Clinical features frequently observed in DME include retinal thickening, cystoid macular edema, serous retinal detachment, vitreomacular traction, and hard exudates [29]. The term ‘clinically significant macular edema’ (CSME) is used in cases where retinal thickening is present at or within 500 μm of the center of the macula or is of at least 1 disk area in size and within 1 disk diameter of the center of the macula, and/or hard exudates are present within 500 μm of the center of the macula with adjacent retinal thickening [29,30]. It is the presence of these features that can cause gradual reduction in visual acuity (VA) [31,32]. CSME is further classified as focal and diffuse DME, based on observations made during clinical investigation [29].

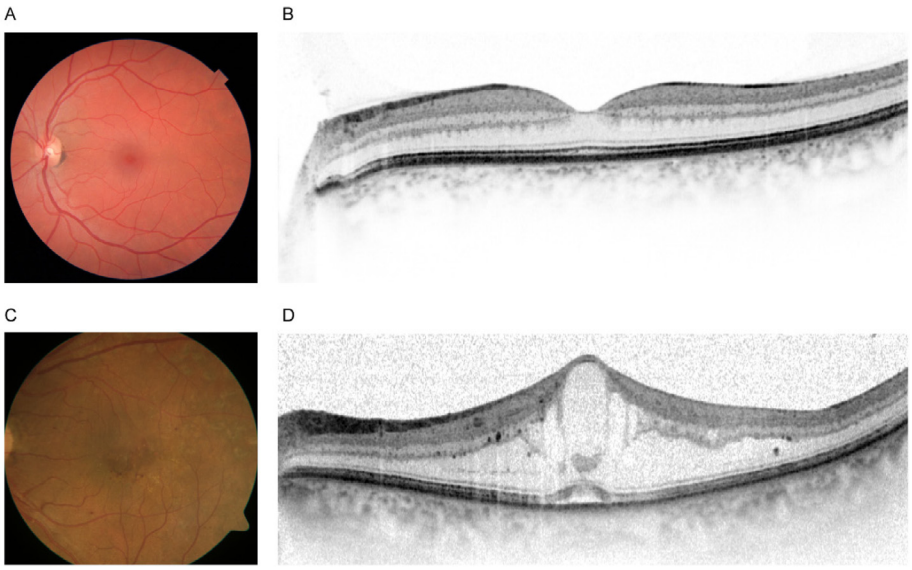

Fig. 1 – Fundus photograph (A) and corresponding optical coherence tomography image (B) of a healthy eye. Fundus photograph (C) and corresponding optical coherence tomography image (D) of an eye with diabetic macular edema.

4. Clinical investigation of DME

In addition to standard fundus photography, used to identify retinal abnormalities (Fig. 1), and best-corrected visual acuity (BCVA) measurement through letter chart testing, several imaging techniques can be used to help to identify and measure the clinical features of DME [3]. Optical coherence tomography can generate a three-dimensional image by shining infrared light on to the retina and analyzing the scatter pattern (Fig. 1) [29,33]. This can help to identify changes in the retina, including retinal thickening, macular edema, and serous retinal detachment [29]. Leakage from blood vessels in the retina can be visualized by injecting fluorescent dye into a patient's bloodstream prior to photographing; this technique is known as fluorescein angiography (FA) [3,29], and is employed to classify focal and diffuse CSME [29]. Focal CSME is diagnosed when distinct points of hyperfluorescence, as a result of microaneurysm leakage, are observed with FA, whereas diffuse CSME is diagnosed if general areas of intraretinal leakage from a retinal capillary bed are observed [29].

5. Available treatment options for DME

A number of therapeutic options are available for the treatment of visual impairment due to DME. For the last three decades, the main treatment for DME has been laser therapy [34]. *Focal laser therapy* is thought to seal microaneurysms and thus help to prevent leakage in cases of focal DME [35]. *Grid laser therapy* is thought to increase oxygen availability to areas of hypoxia by reducing demands elsewhere, and subsequently decrease vasoconstriction [35]. This, in turn, reduces the total area of abnormal leakage, helping to resolve macular edema and re-establish the retinal pigment epithelium [35]. Laser therapy has been successful for stabilizing vision, that is, preventing any further vision loss; however, recovery of full VA following laser therapy is rare [30,34].

Corticosteroid therapy is able to inhibit many of the processes known to be involved in the progression of DME, through anti-inflammatory properties [36] and VEGF inhibition [37]. It is therefore not surprising that intravitreal corticosteroid injections have been shown to be an effective therapy for DME [27,34,38]. Long-acting corticosteroid implants are also available, which have the added benefit of reducing the number and frequency of injections [29,34]. However, an increased chance of pathologic intraocular pressure elevation and cataracts must be taken into account when considering these therapies [28,34,38].

More recently, two anti-VEGF agents have been approved for the treatment of DME [39,40]. Clinical trials in patients with DME have repeatedly shown that anti-VEGF therapy not only stabilizes but also restores vision in a substantial proportion of those treated [25,26].

6. Anti-VEGF agents – mode of action and rationale for use

The human VEGF family comprises a number of related proteins, including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF) [41]. All are able to influence angiogenesis and have key roles in vascular formation and maintenance [41,42]. The normal circulating level of VEGF has protective actions, including maintenance of angiogenesis and endothelial cell integrity [42]. However, people with diabetes may experience increased vasoconstriction and capillary loss within the retina causing hypoxia, upregulation of VEGF, and subsequent increased vascular permeability, one of the key mediators of DME [29]. The effects of VEGF are actioned via specific VEGF receptors (VEGFRs) [41], with each having a separate purpose within a particular tissue [43]. Recently, it has been demonstrated that a single cell can differentially express multiple receptors on different surfaces, thereby generating a particular response dependent not only on the VEGF that is presented, but also the origin of the VEGF

[44]. In the retina, for example, endothelial cells express VEGFR-1 (fms-related tyrosine kinase 1; Flt-1) on the luminal side, which has cytoprotective properties mediated through Akt [44]. The same stimulus presented on the neural side interacts with VEGFR-2 (kinase insert domain receptor; KDR) and stimulates intracellular p38, triggering hyperpermeability [44]. This provides an attractive intravitreal pathophysiologic target that may help to reduce vascular permeability and macular edema in the eye.

Given the important role that VEGF plays in normal vascular homeostasis [41,42], there is particular interest in determining whether intravitreal anti-VEGF injections could have an impact on circulating VEGF. The potential for systemic safety effects are particularly relevant in patients with DME, given their high risk of comorbidities [4,14–16]. Much of the information regarding systemic safety originates from the use of anti-VEGF therapy in oncology services [42]. The role of VEGF in angiogenesis is necessary to perpetuate tumors [45] and systemic anti-VEGF therapy is widely used as a pre-treatment prior to curative surgery to improve patient outcomes [46]. Data collated from this usage has given us valuable information about the effects of systemic VEGF inhibition on other organ systems, including compromised wound healing, increased risk of hypertension and thromboembolic events, cardiac dysfunction, and renal toxicity [42]. Neurogenesis and neuroprotection may also be impaired, which could be a significant problem for someone with diabetes who is already experiencing neuropathy in some form [47]. In the setting of a cancer treatment that improves survival rates, the risks associated with VEGF inhibition are acceptable; however, in the setting of treating a lifelong chronic condition such as diabetes, which is known to adversely affect the vasculature [8], these potential side effects cannot be justified. A greater understanding of the exact mode of action and pathways affected therefore becomes necessary.

These observations are of particular interest when considering the potential systemic exposure of intravitreal anti-VEGF agents in high-risk patients, such as those with DME. A recent pooled safety analysis of ranibizumab and aflibercept in patients with DME ($N = 1078$) has indicated that patients with the highest exposure to anti-VEGF therapy (monthly treatment over 2 years) may have an increased risk for some systemic adverse events (AEs) compared with sham/laser treatment arms [48]. Systemic safety warnings for the potential risk of arterial thromboembolic events (ATEs) are common to both anti-VEGF agents approved for the treatment of DME [39,40]; agents that target VEGF and VEGFR share 'class' effects as a result of systemic VEGF inhibition [42,49]. This is an important aspect to be taken into account when considering a medication for DME; however, the wealth of anti-VEGF safety data from clinical trials in DME, summarized below, is reassuring.

7. Anti-VEGF agents used in the treatment of DME

7.1. *Ranibizumab (LUCENTIS®; Novartis, Basel, Switzerland/Genentech, South San Francisco, CA, USA/ Roche, Basel, Switzerland) [39]*

Ranibizumab is a monoclonal anti-VEGF-A Fab fragment that was specifically developed for intraocular use [39,50]. The design of the molecule maintains the maximum biologic activity while localizing the effects to the eye and minimizing systemic exposure [39,50]. In the eye, ranibizumab inhibits the action of VEGF-A, decreasing vascular permeability and edema [39,50].

Several clinical trials have demonstrated the efficacy and safety profile of ranibizumab in the treatment of patients with DME. The 12-month, phase III RESTORE study compared ranibizumab 0.5 mg monotherapy ($n = 116$) or combined with laser ($n = 118$), with laser alone ($n = 111$) [51]. Mean change in BCVA from baseline to Month 12 was significantly greater with ranibizumab (6.8 ± 8.3 letters; $p < 0.0001$) and ranibizumab with laser (6.4 ± 11.8 letters; $p = 0.0004$) than with laser monotherapy (0.9 ± 11.4 letters) [51]. The initial core study was extended to assess ranibizumab administered using an individualized *pro re nata* (PRN) regimen over 3 years and permitted patients previously receiving laser alone to switch to ranibizumab 0.5 mg PRN [25,51,52]. The RESTORE extension studies demonstrated that patients in the ranibizumab groups maintained their initial BCVA gains through Month 36 and highlighted that early treatment with ranibizumab is key in reducing vision loss [25,52]. The identical 36-month, phase III RIDE and RISE studies ($N = 759$), plus 2-year open-label extension ($N = 500$), similarly demonstrated that ranibizumab induced significant, sustained improvements in visual outcomes [32,49,53].

Importantly, ranibizumab was largely well tolerated in the RESTORE, RISE and RIDE studies [25,32,49,51–53], and other studies assessing its use in patients with DME [54,55]. In RISE and RIDE, rates of systemic side effects were low and similar across ranibizumab and sham treatment groups: 5.6% and 11.9% of patients in the ranibizumab 0.5 mg group in RISE and RIDE, respectively, experienced a serious AE potentially related to inhibition of systemic VEGF, compared with 10.6% and 9.4% in the sham treatment group over 24 months [32]. Causes of death in RISE and RIDE were consistent with those commonly observed in patients with advanced diabetes [32,49,53]. No new ocular or systemic safety findings were observed following long-term ranibizumab use in the 3-year RESTORE study and data were consistent with other DME trials and ranibizumab studies in neovascular age-related macular degeneration and retinal vein occlusion [25]. Real-world use of ranibizumab is currently being monitored in LUMINOUS (NCT01318941), the largest observational trial in ophthalmology [56].

7.2. *Aflibercept (EYLEA®; Bayer HealthCare, Berlin, Germany/Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA) [40]*

Aflibercept is a recombinant anti-VEGF-A/VEGF-B/PlGF fusion protein containing the fragment crystallizable region (Fc) portion of IgG [57]. Aflibercept was initially designed for systemic oncology therapy (metastatic colon cancer) [58], but is also licensed for ocular use [40]. The presence of the Fc portion in aflibercept may permit the molecule to move across the blood–retina barrier and into the systemic circulation, and reductions in systemic VEGF levels have previously been observed following intravitreal aflibercept treatment [59–61]. The efficacy and safety profiles of aflibercept in DME were

assessed in the two parallel, phase III VISTA and VIVID studies (N = 865) [26,62]. Intravitreal aflibercept (2 mg) was associated with significant BCVA gains from baseline over 100 weeks, compared with laser treatment [26]. Despite the potential risk of increased systemic exposure [61], incidences of nonocular AEs in VISTA and VIVID were low and similar across treatment groups [26]. Rates of cerebrovascular accident were slightly higher in the aflibercept group (pooled monthly and bimonthly treatment groups) than the laser control group (2.2% vs 0.7%, respectively), while incidence of acute myocardial infarction and acute cardiac failure was higher in the laser control group than the pooled aflibercept group (2.1% vs 0.9% and 1.4% vs 0.3%, respectively), and no clear trend was observed [26]. The incidence of Anti-Platelet Trialists' Collaboration criteria-defined ATEs were low and equivalent across treatment groups [26].

Further studies of aflibercept are ongoing. ENDURANCE-2 (NCT02368756) will examine the need for further aflibercept treatment in patients after the 3-year VISTA DME endpoint, and the TADI study (NCT02633852) will evaluate the efficacy of a treat-and-extend aflibercept regimen as a second-line treatment for DME.

7.3. *Bevacizumab (AVASTIN®; Genentech/Roche) [63]*

Bevacizumab is a full-length anti-VEGF-A monoclonal antibody that was developed, and is currently approved, as a systemic therapy for several oncology indications [63]. Bevacizumab is not licensed or manufactured for ophthalmic indications but the agent is used off-label for the treatment of retinal disease, including DME [64,65]. As with aflibercept, the inclusion of the Fc portion in the design of the molecule may allow bevacizumab to pass from the vitreous into the systemic circulation [61,66]. Reductions in systemic VEGF levels have been seen after intravitreal bevacizumab treatment [61,66], as well as therapeutic effects in the fellow untreated eye [67].

8. How can we further improve treatment for patients with DME?

While anti-VEGF agents have proven efficacy in providing visual benefits in patients with DME, in order to achieve optimal treatment outcomes, the patient must be considered as a whole. This requires a collaborative approach that ensures prompt treatment for the patient's eye condition as well as proper consideration of systemic comorbidities and potential safety issues.

In addition to selecting the right therapy for each patient, timing of treatment is also important. Because vision loss with DME generally occurs very gradually [31,32], early diagnosis offers the opportunity for early anti-VEGF treatment and the prospect of a more favorable outcome than if treatment was delayed [25,52]. Regular and frequent screening helps to identify DME as early as possible, and timely referral helps to ensure that patients are treated promptly [21]. Nevertheless, help is still needed for patients who already have severe DR or DME and are at risk of losing their vision.

Integrating ophthalmologists into multidisciplinary medical teams that include diabetologists, internists or primary care physicians as well as specialists in comorbidities may help [68,69]. An excellent example of the benefit of a multidisciplinary team is the treatment of people who require a hip replacement following a fall [70]. As most hip fracture patients are elderly, there are other comorbidities to consider, so the teams include orthopedic, geriatric, mental health, bone heath, and falls prevention specialists to assess the best rehabilitation strategy for the patient [70]. Liaison with primary care and social services is also essential to ensure the patient is cared for from inpatient admission through to community rehabilitation [70,71]. The ultimate aim of engaging multidisciplinary teams as early as possible is for the patient to achieve the best possible care and recover quickly whilst minimizing hospital stay, post-treatment complications, and cost [71].

Many patients with DME share the same complex, highly comorbid profile as those with hip fracture; however, collaborations between retinal specialists and other specialists, such as diabetologists, are currently often limited. Although there are examples of multidisciplinary teams for diabetes in general [72,73], they do not yet extend to cover comorbidities in an integrated way. An example of a successful, efficient program for applying integrated, personalized care to the diabetes population is the 'Chronic Care Model', developed in the USA [74]. The model operates on several levels, from working with governing bodies to reorganize and redefine healthcare teams to facilitate access to appropriate care in a coordinated and timely fashion, to educating and encouraging patients in self-management of their condition(s) and forging links between the healthcare system and the community [74]. Evidence of the benefits of applying this model have included increased rates of eye examinations, improved glycemic control, reduced blood pressure and weight, and better clinical outcomes overall [74].

Within the multidisciplinary team, each healthcare professional retains their specialist role, but operates with the aim of working seamlessly with other specialists, such as through joint clinics, as well as other departments to link the hospital, general practice and community. The consultant diabetologist may take a leadership role within the team, to provide specialist clinical advice and co-ordinate the team members [75]. In some cases, implementation of the Chronic Care Model has caused staff roles to change slightly, to improve efficiency [74]. In one example, nurses, instead of primary care physicians, became responsible for performing foot examinations, and as a result, foot care improved [74].

Development and utilization of patient administration systems specifically designed to ensure all of the specialist team members have easy access to data and notes for each patient, and to improve communication between team members, would facilitate more integrated treatment. For example, glycemic targets for each individual that are appropriate to their full clinical picture could be set [74]. Patients may also benefit from their specialists being aware of the potential side effects and interactions between treatments prescribed by their colleagues. Specialists may then be more mindful of potential systemic side effects and be able to identify them more quickly. The Medical Archival Retrieval System is one

example of a fully integrated electronic clinical notes system that stores laboratory test results, medications, comorbidities, and patient visit data [74]; information that can potentially help to avoid AEs and unnecessary clinic visits.

Finally, as evidenced with the Chronic Care Model, patients themselves can also play a large part in their treatment. From the outset, individuals with diabetes and patients with DR/DME should be encouraged to regularly monitor their vision at home and be motivated to help themselves manage their systemic conditions and ensure clinic visit, treatment, and medication compliance.

9. Conclusions

Although the benefit of anti-VEGF agents for improving VA in patients with DME is proven, achieving optimal outcomes will require consideration of the patient as a whole. Using a collaborative approach to patient management could help to ensure early detection and treatment for DME and proper consideration of systemic comorbidities and potential safety issues.

Contributors

WDS conceived the idea of the manuscript. All authors participated in writing the manuscript, provided critical revision of the manuscript for important intellectual content and gave their final approval of the version submitted for publication.

Conflict of interest

None of the authors have any potential conflicts of interest associated with this publication. Outside of this publication, WDS reports personal fees from Novartis Pharma AG, Boehringer Ingelheim, MSD and Pfizer, grants, personal fees and non-financial support from Novo Nordisk, and personal fees and non-financial support from Janssen Pharmaceuticals; FXC reports personal fees from Novartis Pharma AG and is an advisor for Novartis Pharma AG, Astra Zeneca, Boehringer-Ingelheim, Eli Lilly and Takeda; CP reports consultancy fees from Alcon Pharma, Novartis Pharma and Bayer.

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REFERENCES

[1] International Diabetes Federation. IDF Diabetes Atlas 7th Edition, http://www.diabetesatlas.org/component/attachments/?task=download&id=116; 2015 [accessed 01.03.16].

[2] Centers for Disease Control and Prevention. National diabetes fact sheet, http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf; 2011 [accessed 01.03.16].

[3] National Eye Institute, National Institutes of Health. Facts about diabetic retinopathy, http://nei.nih.gov/health/diabetic/retinopathy; 2015 [accessed 13.10.16].

[4] Klein R, Zinman B, Gardiner R, Suissa S, Donnelly SM, Sinaiko AR, et al. The relationship of diabetic retinopathy to preclinical diabetic glomerulopathy lesions in type 1 diabetic patients: the Renin-Angiotensin System Study. Diabetes 2005;54:527–33. http://dx.doi.org/10.2337/diabetes.54.2.527.

[5] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86. http://dx.doi.org/10.1056/NEJM199309303291401.

[6] Chan JC, Gagliardino JJ, Baik SH, Chantelot JM, Ferreira SR, Hancu N, et al. Multifaceted determinants for achieving glycemic control: the International Diabetes Management Practice Study (IDMPS). Diabetes Care 2009;32:227–33. http://dx.doi.org/10.2337/dc08-0435.

[7] Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. Diabet Med 2012;29:682–9. http://dx.doi.org/10.1111/j.1464-5491.2012.03605.x.

[8] Long AN, Dagogo-Jack S. Comorbidities of diabetes and hypertension: mechanisms and approach to target organ protection. J Clin Hypertens (Greenwich) 2011;13:244–51. http://dx.doi.org/10.1111/j.1751-7176.2011.00434.x.

[9] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–12. http://dx.doi.org/10.1136/bmj.321.7258.405.

[10] Strain WD, Cos X, Hirst M, Vencio S, Mohan V, Voko Z, et al. Time to do more: addressing clinical inertia in the management of type 2 diabetes mellitus. Diabetes Res Clin Pract 2014;105:302–12. http://dx.doi.org/10.1016/j.diabres.2014.05.005.

[11] Pramming S, Thorsteinsson B, Bendtson I, Binder C. The relationship between symptomatic and biochemical hypoglycaemia in insulin-dependent diabetic patients. J Intern Med 1990;228:641–6. http://dx.doi.org/10.1111/j.1365-2796.1990.tb00292.x.

[12] Minassian DC, Owens DR, Reidy A. Prevalence of diabetic macular oedema and related health and social care resource use in England. Br J Ophthalmol 2012;96:345–9. http://dx.doi.org/10.1136/bjo.2011.204040.

[13] Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556–64. http://dx.doi.org/10.2337/dc11-1909.

[14] Targher G, Bertolini L, Tessari R, Zenari L, Arcaro G. Retinopathy predicts future cardiovascular events among type 2 diabetic patients: the Valpolicella Heart Diabetes Study. Diabetes Care 2006;29:1178. http://dx.doi.org/10.2337/diacare.2951178.

[15] van Hecke MV, Dekker JM, Stehouwer CD, Polak BC, Fuller JH, Sjolie AK, et al. Diabetic retinopathy is associated with mortality and cardiovascular disease incidence: the EURODIAB prospective complications study. Diabetes Care 2005;28:1383–9. http://dx.doi.org/10.2337/diacare.28.6.1383.

[16] Venkatesh P, Tibrewal S, Bhowmik D, Tripathi M, Ramakrishnan S, Vashist N, et al. Prevalence of systemic co-morbidities in patients with various grades of diabetic retinopathy. Indian J Med Res 2014;140:77–83.
[17] Nguyen-Khoa BA, Goehring EL, Werther W, Fung AE, Do DV, Apte RS, et al. Hospitalized cardiovascular events in patients with diabetic macular edema. BMC Ophthalmol 2012;12:11. http://dx.doi.org/10.1186/1471-2415-12-11.
[18] Shrestha GS, Kaiti R. Visual functions and disability in diabetic retinopathy patients. J Optom 2014;7:37–43. http://dx.doi.org/10.1016/j.optom.2013.03.003.
[19] NHS. Type 2 diabetes – treatment, http://www.nhs.uk/conditions/diabetes-type2/Pages/Treatment.aspx; 2014 [accessed 01.04.16].
[20] American Diabetes Association. Your health care team, http://www.diabetes.org/living-with-diabetes/treatment-and-care/whos-on-your-health-care-team/your-health-care-team.html; 2015 [accessed 01.04.16].
[21] International Diabetes Federation and The Fred Hollows Foundation. Diabetes eye health: a guide for health care professionals, http://www.idf.org/eyecare; 2015 [accessed 01.09.16].
[22] Seidu S, Walker NS, Bodicoat DH, Davies MJ, Khunti K. A systematic review of interventions targeting primary care or community based professionals on cardio-metabolic risk factor control in people with diabetes. Diabetes Res Clin Pract /sb:maintitle> 2016;113:1–13. http://dx.doi.org/10.1016/j.diabres.2016.01.022.
[23] Bodicoat DH, Mundet X, Davies MJ, Khunti K, Roura P, Franch J, et al. The impact of a programme to improve quality of care for people with type 2 diabetes on hard to reach groups: the GEDAPS study. Prim Care Diabetes 2015;9:211–8. http://dx.doi.org/10.1016/j.pcd.2014.08.001.
[24] UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–13. http://dx.doi.org/10.1136/bmj.317.7160.703.
[25] Schmidt-Erfurth U, Lang GE, Holz FG, Schlingemann RO, Lanzetta P, Massin P, et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. Ophthalmology 2014;121:1045–53. http://dx.doi.org/10.1016/j.ophtha.2013.11.041.
[26] Brown DM, Schmidt-Erfurth U, Do DV, Holz FG, Boyer DS, Midena E, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. Ophthalmology 2015;122:2044–52. http://dx.doi.org/10.1016/j.ophtha.2015.06.017.
[27] Boyer DS, Yoon YH, Belfort Jr R, Bandello F, Maturi RK, Augustin AJ, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 2014;121:1904–14. http://dx.doi.org/10.1016/j.ophtha.2014.04.024.
[28] Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology 2012;119:2125–32. http://dx.doi.org/10.1016/j.ophtha.2012.04.030.
[29] Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. Surv Ophthalmol 2009;54:1–32. http://dx.doi.org/10.1016/j.survophthal.2008.10.001.
[30] Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796–806. http://dx.doi.org/10.1001/archopht.1985.01050120030015.
[31] Cunningham Jr ET, Adamis AP, Altaweel M, Aiello LP, Bressler NM, D'Amico DJ, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005;112:1747–57. http://dx.doi.org/10.1016/j.ophtha.2005.06.007.
[32] Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789–801. http://dx.doi.org/10.1016/j.ophtha.2011.12.039.
[33] Nioka S, Chen Y. Optical technology developments in biomedicine: history, current and future. Transl Med UniSa 2011;1:51–150.
[34] Royal College of Ophthalmologists. Diabetic retinopathy guidelines, http://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-301-FINAL-DR-GUIDELINES-DEC-2012-updated-July-2013.pdf; 2012 [accessed 01.06.15].
[35] Romero-Aroca P, Reyes-Torres J, Baget-Bernaldiz M, Blasco-Sune C. Laser treatment for diabetic macular edema in the 21st century. Curr Diabetes Rev 2014;10:100–12. http://dx.doi.org/10.2174/1573399810666140402123026.
[36] Sohn HJ, Han DH, Kim IT, Oh IK, Kim KH, Lee DY, et al. Changes in aqueous concentrations of various cytokines after intravitreal triamcinolone versus bevacizumab for diabetic macular edema. Am J Ophthalmol 2011;152:686–94. http://dx.doi.org/10.1016/j.ajo.2011.03.033.
[37] Brooks Jr HL, Caballero Jr S, Newell CK, Steinmetz RL, Watson D, Segal MS, et al. Vitreous levels of vascular endothelial growth factor and stromal-derived factor 1 in patients with diabetic retinopathy and cystoid macular edema before and after intraocular injection of triamcinolone. Arch Ophthalmol 2004;122:1801–7. http://dx.doi.org/10.1001/archopht.122.12.1801.
[38] Campochiaro PA, Brown DM, Pearson A, Ciulla T, Boyer D, Holz FG, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Ophthalmology 2011;118:626–635 e2. http://dx.doi.org/10.1016/j.ophtha.2010.12.028.
[39] Novartis. LUCENTIS® Summary of Product Characteristics, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000715/WC500043546.pdf; 2014 [accessed 01.06.15].
[40] Bayer. EYLEA® Summary of Product Characteristics, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002392/WC500135815.pdf; 2015 [accessed 01.06.15].
[41] Holmes DI, Zachary I. The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. Genome Biol 2005;6:209. http://dx.doi.org/10.1186/gb-2005-6-2-209.
[42] Chen HX, Cleck JN. Adverse effects of anticancer agents that target the VEGF pathway. Nat Rev Clin Oncol 2009;6:465–77. http://dx.doi.org/10.1038/nrclinonc.2009.94.
[43] Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J 1999;13:9–22.
[44] Hudson N, Powner MB, Sarker MH, Burgoyne T, Campbell M, Ockrim ZK, et al. Differential apicobasal VEGF signaling at vascular blood-neural barriers. Dev Cell 2014;30:541–52. http://dx.doi.org/10.1016/j.devcel.2014.06.027.
[45] Yadav L, Puri N, Rastogi V, Satpute P, Sharma V. Tumour angiogenesis and angiogenic inhibitors: a review. J Clin Diagn Res 2015;9:XE01–5. http://dx.doi.org/10.7860/JCDR/2015/12016.6135.
[46] Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.

N Engl J Med 2004;350:2335–42. http://dx.doi.org/10.1056/NEJMoa032691.
[47] Mackenzie F, Ruhrberg C. Diverse roles for VEGF-A in the nervous system. Development 2012;139:1371–80. http://dx.doi.org/10.1242/dev.072348.
[48] Avery RL, Gordon GM. Systemic safety of prolonged monthly anti-vascular endothelial growth factor therapy for diabetic macular edema: a systematic review and meta-analysis. JAMA Ophthalmol 2016;134:21–9. http://dx.doi.org/10.1001/jamaophthalmol.2015.4070.
[49] Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology 2013;120:2013–22. http://dx.doi.org/10.1016/j.ophtha.2013.02.034.
[50] Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 2006;26:859–70. http://dx.doi.org/10.1097/01.iae.0000242842.14624.e7.
[51] Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615–25. http://dx.doi.org/10.1016/j.ophtha.2011.01.031.
[52] Lang GE, Berta A, Eldem BM, Simader C, Sharp D, Holz FG, et al. Two-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema: interim analysis of the RESTORE extension study. Ophthalmology 2013;120:2004–12. http://dx.doi.org/10.1016/j.ophtha.2013.02.019.
[53] Boyer DS, Nguyen QD, Brown DM, Basu K, Ehrlich JSRide and Rise Research Group. Outcomes with as-needed ranibizumab after initial monthly therapy: long-term outcomes of the Phase III RIDE and RISE trials. Ophthalmology 2015;122:2504–2513 e1. http://dx.doi.org/10.1016/j.ophtha.2015.08.006.
[54] Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, Larsen M, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care 2010;33:2399–405. http://dx.doi.org/10.2337/dc10-0493.
[55] Prunte C, Fajnkuchen F, Mahmood S, Ricci F, Hatz K, Studnicka J, et al. Ranibizumab 0.5 mg treat-and-extend regimen for diabetic macular oedema: the RETAIN study. Br J Ophthalmol 2016;100:787–95. http://dx.doi.org/10.1136/bjophthalmol-2015-307249.
[56] Holz FG, Bandello F, Gillies M, Mitchell P, Osborne A, Sheidow T, et al. Safety of ranibizumab in routine clinical practice: 1-year retrospective pooled analysis of four European neovascular AMD registries within the LUMINOUS programme. Br J Ophthalmol 2013;97:1161–7. http://dx.doi.org/10.1136/bjophthalmol-2013-303232.
[57] Trichonas G, Kaiser PK. Aflibercept for the treatment of age-related macular degeneration. Ophthalmol Ther 2013;2:89–98. http://dx.doi.org/10.1007/s40123-013-0015-2.
[58] Regeneron. ZALTRAP® Summary of Product Characteristics, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002532/WC500139484.pdf; 2013 [accessed 01.03.16].
[59] Wang X, Sawada T, Sawada O, Saishin Y, Liu P, Ohji M. Serum and plasma vascular endothelial growth factor concentrations before and after intravitreal injection of aflibercept or ranibizumab for age-related macular degeneration. Am J Ophthalmol 2014;158:738–744 e1. http://dx.doi.org/10.1016/j.ajo.2014.06.009.
[60] Zehetner C, Kralinger MT, Modi YS, Waltl I, Ulmer H, Kirchmair R, et al. Systemic levels of vascular endothelial growth factor before and after intravitreal injection of aflibercept or ranibizumab in patients with age-related macular degeneration: a randomised, prospective trial. Acta Ophthalmol 2015;93:e154–9. http://dx.doi.org/10.1111/aos.12604.
[61] Avery RL, Castellarin AA, Steinle NC, Dhoot DS, Pieramici DJ, See R, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab, or aflibercept in patients with DME. Association for Research in Vision and Ophthalmology. Orlando, FL, USA, May 4–8, 2014. Poster 586.
[62] Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology 2014;121:2247–54. http://dx.doi.org/10.1016/j.ophtha.2014.05.006.
[63] Roche. AVASTIN® Summary of Product Characteristics, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf; 2013 [accessed 01.06.15].
[64] Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmology 2010;117:1078–1086 e2. http://dx.doi.org/10.1016/j.ophtha.2010.03.045.
[65] Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, Sanchez JG, Wu L, Maia M, et al. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. Ophthalmology 2007;114:743–50. http://dx.doi.org/10.1016/j.ophtha.2006.12.028.
[66] Matsuyama K, Ogata N, Matsuoka M, Wada M, Takahashi K, Nishimura T. Plasma levels of vascular endothelial growth factor and pigment epithelium-derived factor before and after intravitreal injection of bevacizumab. Br J Ophthalmol 2010;94:1215–8. http://dx.doi.org/10.1136/bjo.2008.156810.
[67] Bakbak B, Ozturk BT, Gonul S, Yilmaz M, Gedik S. Comparison of the effect of unilateral intravitreal bevacizumab and ranibizumab injection on diabetic macular edema of the fellow eye. J Ocul Pharmacol Ther 2013;29:728–32. http://dx.doi.org/10.1089/jop.2013.0049.
[68] Advocating for improved treatment and outcomes for diabetic macular edema: a report based on an international expert summit convened in Paris, June 2014, http://www.angio.org/wp-content/uploads/2014/02/DME-Intl-Summit-White-Paper-Report.pdf; 2014 [accessed 01.06.15].
[69] Centers for Disease Control and Prevention. Working together to manage diabetes: a toolkit for pharmacy, podiatry, optometry, and dentistry (PPOD), http://www.cdc.gov/diabetes/ndep/ppod.htm; 2014 [accessed 01.06.15].
[70] National Institute for Health and Care Excellence. The management of hip fracture in adults: NICE clinical guideline 124, http://www.nice.org.uk/guidance/cg124/resources/guidance-hip-fracture-pdf; 2011 [accessed 01.06.15].
[71] Khan F, Ng L, Gonzalez S, Hale T, Turner-Stokes L. Multidisciplinary rehabilitation programmes following joint replacement at the hip and knee in chronic arthropathy. Cochrane Database Syst Rev 2008:CD004957. http://dx.doi.org/10.1002/14651858.CD004957.pub3.
[72] Tapp H, Phillips SE, Waxman D, Alexander M, Brown R, Hall M. Multidisciplinary team approach to improved chronic care management for diabetic patients in an urban safety net ambulatory care clinic. J Am Board Fam Med 2012;25:245–6. http://dx.doi.org/10.3122/jabfm.2012.02.110243.
[73] Northamptonshire Healthcare NHS Foundation Trust. Diabetes multidisciplinary team, http://www.nht.nhs.

uk/main.cfm?type=DIABETESMULTIDISCI; 2016 [accessed 01.04.16].

[74] Stellefson M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. Prev Chronic Dis 2013;10:E26. http://dx.doi.org/10.5888/pcd10.120180.

[75] Diabetes UK. Commissioning Specialist Diabetes Services for Adults with Diabetes: A Diabetes UK Task and Finish Group Report, https://www.diabetes.org.uk/Upload/Reports/Defining%20Specialist%20Diabetes%20Service%20For%20Adults%20with%20Diabetes.doc; 2010 [accessed 16.12.16].