# Efficacy and follow-up of anti-VEGF injections in diabetic macular edema in real-life practice at the Dijon university medical centre through the Save Sight Registries

Mélanie Tessier, C. Meillon, Catherine Creuzot-Garcher, Alain M. Bron, P. Nguyen

# Efficiency and follow-up of anti-VEGF injections in diabetic macular edema in real-life practice through the Save Sight Registries

# Efficacité et suivi des injections d'anti-VEGF dans l'œdème maculaire diabétique, une étude de vraie vie au CHU de Dijon grâce au Save Sight Registries

## Anti-VEGF injections in diabetic macular edema in real-life practice

Tessier M.[1], Meillon C.[1], Creuzot-Garcher C.[1,2], Bron AM.[1,2] and Nguyen P.[3]

[1] Service d'Ophtalmologie, CHU de Dijon, France

[2] Eye and Nutrition Research Group, CSGA, UMR1324 INRA, 6265 CNRS, Université Bourgogne Franche-Comté, Dijon, France

[3] The Save Sight Institute, Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia

**Efficacy and follow-up of anti-VEGF injections in diabetic macular edema in real-life practice at the Dijon university medical center through the Save Sight Registries**

**Efficacité et suivi des injections d'anti-VEGF dans l'œdème maculaire diabétique, une étude de vraie vie au CHU de Dijon grâce au Save Sight Registries**

**Anti-VEGF injections in diabetic macular edema in real-life practice**

**Injections d'anti-VEGF dans l'œdème maculaire diabétique en vraie-vie**

**Abstract**

**Purpose**

To evaluate the efficacy of intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections (IVT) in diabetic macular edema (DME) in real-life practice using the Save Sight Registries (SSR).

**Material and Methods**

We conducted an observational, single-center, retrospective study in the department of ophthalmology of the Dijon University Hospital. We included treatment-naive patients who presented with DME between January 2016 and December 2017. Demographic and clinical data, follow-up visits, and treatments administered were entered into the SSR, an international online ophthalmic registry. Primary endpoints were the change in best-corrected visual acuity (BCVA) and central subfield thickness (CST) from baseline to 12 and 24 months.

**Results**

Fifty-eight eyes of 43 patients with a mean [standard deviation (SD)] age of 67.1 [9.5] years were included. Forty-one eyes completed 12 months of follow-up, and 17 eyes completed 24 months of follow up. Median [SD] baseline BCVA was 56.1 [22.9] ETDRS letters and the median [95% confidence interval (95% CI)] baseline CST was 447.9 [161.0] micrometers (μm). Median [95% CI] improvement in BCVA from baseline to months 12 and 24 were, respectively, +5.6 [+0.5; +10.7] ETDRS letters and +7.7 [−2.8; +18.2] ETDRS letters. The median [95% CI] decrease in CST from baseline to months 12 and 24 were, respectively, -110.9 [-154.5; -67.3] μm and -125.5 [-198.0; -53.0] μm.

**Conclusion**

Our clinical practice can be evaluated easily with the SSR system. In real life, anti-VEGF IVT are an effective treatment for DME which result in improved BCVA and decreased CST.

**Keywords:** Diabetic macular edema, anti-VEGF, Real-life studies, Save Sight Registries

**Résumé**

**Objectif**

Evaluer l'efficacité des injections d'anti-VEGF et nos pratiques dans l'œdème maculaire diabétique (OMD) en vrai-vie grâce à l'utilisation du Save Sight Registries (SSR).

**Matériels et méthodes**

Il s'agit d'une étude observationnelle, monocentrique, rétrospective réalisée dans le service d'ophtalmologie du CHU de Dijon incluant les patients traités pour un OMD entre janvier 2016 et décembre 2017. Les données cliniques et démographiques, les visites de suivi, les traitements administrés ont été implémentés sur la plateforme internet du SSR. Les critères de jugement principaux étaient l'évolution de la meilleure acuité visuelle corrigée (MAVC) et de l'épaisseur centrale fovéolaire (ECF) entre l'inclusion et les visites à 12 mois et 24 mois.

**Résultats**

Cinquante-huit yeux de 43 patients d'âge moyen [déviation standard] de 67,1 [9,5] ans ont été inclus. Quarante et un yeux ont poursuivi un suivi de 12 mois et 17 yeux de 24 mois. La médiane [DS] de la MAVC initiale était de 56,1 [22,9] lettres ETDRS et la médiane [intervalle de confiance 95% (IC 95%)] de l'ECF initiale était de 447,9 [161,0] micromètres (µm). Le gain médian [IC 95%] de la MAVC entre l'inclusion et le mois 12 et 24 était respectivement de +5,6 [+0,5; +10,7] et de +7,7 [−2,8; +18,2] lettres ETDRS. La diminution médiane [IC 95%] de l'ECF entre l'inclusion et le mois 12 et 24 était respectivement de -110,9 [-154,5; -67,3] et de -125,5 [-198,0; -53,0] µm.

**Conclusion**

Le SSR est utile pour l'évaluation de nos pratiques. Les injections d'anti-VEGF sont un traitement efficace de l'OMD.

**Mots-clés :** Oedème maculaire diabétique, anti-VEGF, étude de vrai-vie**,** Save Sight Registries

## Introduction

In France, 3.3 million patients, which is almost 5% of the population, suffer from diabetes mellitus [1]. Diabetic macular edema (DME) is the most frequent cause of visual loss, and its prevalence is about 3% according to recent studies [2–4]. For these patients, DME can lead to a permanent decrease in visual acuity, impairing quality of life [5]. Thus, treatment of DME is a major public health challenge.

DME treatment consists in optimum control of diabetes and blood pressure [6] as well as therapeutic treatment. In most cases, intravitreal injections (IVT) are used. There are two available therapeutic classes: anti-vascular endothelial growth factor (anti VEGF) and corticosteroids [7]. The efficacy and the safety of anti-VEGF IVT has already been demonstrated in DME, with an increase in best-corrected visual acuity (BCVA) and a decrease in central subfield thickness (CST) [8,9].

The evaluation of real-life practices is an essential means of improving patient outcomes. Being able to access to the data of millions of patients has improved our knowledge of retinal diseases. This access has been facilitated by international specialist web platforms such as the Save Sight Registries (SSR). One of its landmark projects is The Fight Retinal Blindness! (FRB!) Project, which was created in order to investigate the safety, effectiveness and adverse effects of treatments in macular diseases [10].

The purpose of this study was to evaluate the efficacy of treatment and our practice in patients treated with anti-VEGF IVT in DME using the SSR.

## Material and methods

### Design

We conducted an observational, monocentric, retrospective study in the ophthalmology department of the Dijon University Hospital. We included patients presenting with DME from January 2016 to December 2017 and treated with anti-VEGF IVT.

### Study population

Treatment-naive patients with type 1 or type 2 diabetes mellitus, suffering from clinically significant diabetic macular edema (CSME) were included. CSME was defined by Early Treatment Diabetic Retinopathy Study (ETDRS) as an edema within 500 micrometers (μm) involving the center of the fovea, or at least one disc area of swelling, any part of which was within the disc diameter of the center of the fovea [11]. Patient co-morbidities, demographics and medical data were collected. One or both eyes were included for each patient. We only analyzed patients who were followed-up for a minimum of one year. All patients under the age of 18 or those presenting with other causes of macular edema were excluded.

### Tools

We used FRB! on the SSR web platform to collect data for each visit, injection, procedure or surgery during the follow-up. The web interface provided a standardized form that was filled out retrospectively.

### Endpoints

The primary endpoints were changes in BCVA and CST from baseline to 12 and 24 months. BCVA were evaluated with the ETDRS chart and CST were measured with Spectral-Domain Optical Coherence Tomography (SD-OCT) (Cirrus®,

Carl Zeiss Meditec Dublin, CA, USA). The secondary endpoints were the number of visits and injections, the re-treatment interval, the proportion of good functional responder eyes (defined as an eye recovering ≥ 80 ETDRS letters during the first year of follow-up) and outcomes with ranibizumab and aflibercept. Number of visits included baseline visits, follow-up visits, injections, procedures like retinal laser or capsulotomy and surgeries. Safety issues focused on adverse events including endophthalmitis, neovascular complications (pre-retinal vitreous hemorrhage, retinal detachment, rubeosis), and complications linked to improved intra ocular pressure (laser trabeculoplasty, incisional glaucoma surgery, starting new glaucoma medication). Moreover, surgeries like cataract extraction and pars plana vitrectomy were recorded.

**Statistical analysis**

Results were expressed as means with standard deviations (SD) or 95% confidence intervals (95% CI) if variables were continuous. If variables were categorical, results were expressed as medians with interquartile ratios (IQR) or as percentages (%). Analyses were performed using R Statistical Software, version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

A total of 119 eyes belonging to 88 patients suffering from DME were treated by anti-VEGF IVT between January 2016 and December 2017 in the ophthalmology department of the Dijon University Hospital. Among them, 58 eyes of 43 patients were included with a minimum of 1 year of follow-up, and 17 patients completed 2 years of follow-up. At baseline, the mean [SD] age was 67.1 [9.5] years, the mean [SD] diabetes duration was 12.2 [7.3] years and the mean [SD] HbA1c level was 8.4 [2.3] %. Diabetic retinopathy (DR) was diagnosed as mild non-proliferative (NPDR) in 7 [12.1%] eyes, moderate NPDR in 10 [17.2%] eyes, severe NPDR in 24 [41.4%] eyes. It was diagnosed as proliferative DR (PDR) non-high-risk in 9 [15.5%] eyes and PDR high-risk in 8 [13.8%] eyes. Baseline demographic and clinical characteristics of the patients are presented in *Table 1.*

At baseline, the mean [SD] BCVA was 56.1 [22.9] ETDRS letters. The mean [95% CI] increase in BCVA from baseline to month 12 and 24 were +5.6 [+0.5; +10.7] ETDRS letters and +7.7 [−2.8; +18.2] ETDRS letters respectively. At baseline, the mean [SD] CST was 447.9 [161.0] µm. Mean [95%CI] decrease in CST from baseline to month 12 and 24 were -110.9 [-154.5; -67.3] µm and -125.5 [-198.0; -53.0] µm, respectively. Visual and anatomical outcomes are presented in *Table 2*. The distribution of BCVA and CST outcomes at baseline versus 12 and 24 months is shown in *Figure 1.*

Twenty-one [36.2%] eyes were good functional responders and recovered 80 ETDRS letters or more during the first year of follow-up.

The median [IQR] number of visits was 15.5 [13.0; 19.8] including 8.0 [6.0; 10.0] injections with a treatment interval of 39.3 [32.5; 47.4] days during the first year.

Twenty-two [37.9%] eyes received ranibizumab and 36 [62.1%] eyes aflibercept during the first year. At baseline, the mean [SD] BCVA was 61.4 [18.5] ETDRS letters in ranibizumab group and 52.8 [24.9] ETDRS letters in aflibercept group. Mean [SD] BCVA at the 1-year visit was 62.5 [24.5] ETDRS letters with ranibizumab and 61.2 [20.9] ETDRS letters with aflibercept. Mean [95% CI] improvement of BCVA from baseline was +1.1 [-4.9; +7.1] ETDRS letters with ranibizumab and +8.4 [+0.9; 15.8] ETDRS letters with aflibercept. Mean [95% CI] CST decreased by -103.4 [-154.5; -52.3] µm with ranibizumab and - 115.6 [-181.3; -49.9] µm with aflibercept (*Table 3*).

During the second year, the median [IQR] number of visits was 6.5 [3.2; 8.5] including 2.5 [0.5; 6.7] injections with a treatment interval of 63.8 [35.8; 132.5] days. From baseline to time point 24 months, the median [IQR] number of visits was 23.0 [18.0; 27.0] including 11.0 [8.0; 15.0] injections with a treatment interval of 48.6 [36.8; 66.6] days. Finally, during the second year, 8 [47.1%] eyes received ranibizumab and 9 [52.9%] eyes aflibercept. Mean [SD] BCVA at the 2-year visit was 62.2 [26.1] ETDRS letters with ranibizumab and 65.6 [17.6] ETDRS letters with aflibercept. Mean [95% CI] improvement of BCVA from baseline was +2.8 [-5.1; +10.6] ETDRS letters with ranibizumab and +12.1 [-8.3; +32.5] ETDRS letters with aflibercept. Mean [95% CI] decrease in CST was -148.3 [-253.3; -43.3] µm with ranibizumab and -107.8 [-227.4; -11.9] µm with aflibercept.

Pro re nata (PRN) regimens with a loading dose (3 or 5 monthly injections) were used in 52 [89.7%] eyes, and treat and extend (T&E) regimens were used in 6 [10.3%] eyes.

For adverse events, we reported pre-retinal vitreous hemorrhage in 1 [1.7%] eye. During follow-up, 10 [17.2%] eyes underwent cataract extraction and 5 [8.6%] eyes underwent pars plana vitrectomy. Adverse events and procedures are shown in *Table 4.*

## Discussion

Our results confirmed the efficacy of anti-VEGF in the treatment of DME in a real-life setting. After 12 and 24 months of follow-up, we observed an increase in BCVA and a decrease in CST in patients receiving anti-VEGF treatment.

Overall, our results are consistent with the scientific literature though the mean BCVA gain and CST decrease were lower than what has been reported in major studies. For aflibercept (VISTA and VIVID studies), the reported mean gain in BCVA from baseline to 1-year was more than 10 ETDRS letters and the mean reduction in CST was more than 180 μm [12]. For ranibizumab (RISE and RIDE studies), the mean change in BVCA from baseline 2-year was more than 11 ETDRS letters and the mean change in CST was more than 250 μm [13]. Our baseline characteristics were not the same as those outlined in the major studies. For instance, our patients were older (mean age of 67.1 years), whereas younger age can predict higher visual acuity gain after anti-VEGF therapy [14]. Baseline BCVA in our study (56.1 ETDRS letters) was comparable to randomized trials. The low number of injections in our study (11.0 injections at 2 years) could explain the low BCVA; in VISTA/VIVID and RISE/RIDE studies the mean numbers of injections were over 20 [12,13]. However, clinical trials impose strict schedules for treatment and follow-up as well as population selection criteria, all of which may lead to better outcomes.

When compared with observational real-life studies, our results were similar or better. In the POLARIS study, a multi-country study of 804 patients, the number of injections and the mean change in BCVA and CST were similar at 12 months (the mean number of injections was 4.9, the mean change BCVA was +4.4 letters, and the mean change in CST was -115.2 μm) [15]. In the OCEAN study, which included

1226 eyes in Germany, the mean number of injections (5.5) and the mean change in BCVA (+ 5.2 ETDRS letters) at 24 months were also similar to our study [16]. In a French study of 72 eyes treated over 12 months: the mean number of injections was 5.3, the mean BCVA gain from baseline was +6.9 ETDRS letters, and the mean reduction in CST was -108.1 μm [17]. When compared with a Danish study of 566 treated eyes, our functional outcomes were higher. Authors reported on mean number of injections was 6.1 and 3.0 during the first and second year, respectively, the mean BCVA gain was +2.7 ETDRS letters, and the mean reduction in CST was -106.9 μm at the 2-year consultation [18].

The number of eyes treated with ranibizumab and with aflibercept was too small to compare their effect. Final BCVA and CST appeared to be similar in the ranibizumab and aflibercept groups. In the aflibercept group, baseline BCVA was lower and CST was higher, which could explain the more significant variations in BCVA and CST in this group. Ranibizumab and aflibercept have been found to have equal outcomes in several other real-life studies as well [19,20].

In our study, T&E was rarely used, with only 6 [10.3%] patients treated with this regimen. The regimen used in most observational studies was the PRN approach. Randomized clinical trials have demonstrated that a T&E regimen was not inferior to a PRN regimen, reporting similar visual and anatomic gains. Moreover, T&E regimens require fewer follow-up visits despite slightly more injections, providing a lower treatment burden and improved treatment compliance [21,22]. Few real-life cohorts investigating T&E in DME are currently available to corroborate the results of randomized clinical trials [23].

We observed an acceptable safety profile. Cataract extraction was performed in 10 patients [17.2%] and pars plana vitrectomy in 5 patients [8.6%]. In major

studies, the most side effect reported at 2 years was cataract (1.7% for aflibercept and 1.6% for ranibizumab) [12,13]. Increased intra-ocular pressure was documented with ranibizumab in RESOLVE and RISE/RIDE studies [8,13], but we were not able to confirm these findings.

The FRB! Project was established in 2009. This web-based system forms the core structure for the Save Sight Registries database. Their interface makes it possible to do a complete follow-up of patients with neovascular age-related macular degeneration, choroidal neovascularization, retinal vein occlusion or diabetic retinopathy. After recording the data relative to visits, injections, procedures and adverse effects, clinicians are provided with a chart with patient details and history of consultations (*Figure 2*) [10]. It can be an interesting tool to enhance patient management and to perform self-audits of our practices. We observed some limitations in data recording. For instance, details about treatment regimen and the morphological features of DME were not required. Hence, in our study data about regimen of treatment has been collected independently. However, this platform was conceived to investigate the safety, the effectiveness and the possible adverse effects of new treatments. In addition, the platform promotes international scientific research collaboration, and more than 30 scientific publications including multi country cohorts have resulted from the FRB! Project.

Observational real-life studies are needed to corroborate results from major controlled and randomized trials, and this type of study can be a powerful tool to improve clinical practice and to define guidelines. A 2017 report commissioned by the French Ministry of Health has reiterated the importance and the benefits of real-life studies and tried to develop strategies to promote their use [24].

We acknowledge several limitations to this study. First, it was a retrospective study with monocentric data collection. Second, the baseline sample size and the number of patients who completed 2 years of follow-up were small. The strength of our study lies in its real-life approach, including strict follow-up of treatment-naive patients with a long follow-up period. Our aim was to use SSR to analyze our practice.

## Conclusion

In summary, SSR has made it possible to evaluate our clinical practice and to share data internationally. In real life, anti-VEGF IVT is an effective treatment for DME, resulting in an improved BCVA and a decrease in CST.

**Figure 1.** Distribution of BCVA and CST outcomes at baseline versus 12 and 24 months

**Figure 2.** Chart with patient data and consultation history

**Table 1** Characteristics at baseline for all eyes included and treated with anti-VEGF.

| Characteristics | |
|---|---|
| Eyes | 58 |
| Patients | 43 |
| Age, years [a] | 67.1 (9.5) |
| Gender, % patients female | 37.2 |
| Diabetes duration, years [a] | 12.2 (7.3) |
| Diabetes type, % patients | |
| Type 1 | 4.7 |
| Type 2 | 95.3 |
| HbA1c level, % [a] | 8.4 (2.3) |
| CSME activity [b] | |
| Centre-involving CSME | 52 (89.7) |
| Non centre-involving CSME | 6 (10.3) |
| Visual acuity, ETDRS letters [a] | 56.1 (22.9) |
| CST, μm [a] | 447.9 (161.0) |
| Severity of retinopathy [b] | |
| Mild NPDR | 7 (12.1) |
| Moderate NPDR | 10 (17.2) |
| Severe NPDR | 24 (41.4) |
| PDR non-high risk | 9 (15.5) |
| PDR high risk | 8 (13.8) |
| Lens status [b] | |
| Pseudophakic | 12 (20.7) |
| Others | 46 (79.3) |

CSME: clinically significant macular edema; CST: central subfield thickness; μm: micrometers; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; SD: standard deviation
[a] mean (standard deviation)
[b] number (%)

**Table 2** Visual and anatomical outcomes for eye completing 1 or 2 years of follow-up.

| Time Point | Outcomes | |
|---|---|---|
| 12 months | Eyes | 58 |
| | Baseline BCVA, ETDRS letters [a] | 56.1 (22.9) |
| | Final BCVA, ETDRS letters [a] | 61.7 (22.2) |
| | BCVA change, ETDRS letters [b] | +5.6 (+0.5; +10.7) |
| | Good functional responders [c] | 21 (36.2) |
| | Baseline CST, μm [a] | 447.9 (161.0) |
| | Final CST, μm [a] | 337.0 (104.2) |
| | CST change, μm [b] | -110.9 (-154.5; -67.3) |
| | Visits [d] | 15.5 (13.0; 19.8) |
| | Injections [d] | 8.0 (6.0; 10.0) |
| | Treatment interval, days [d] | 39.3 (32.5; 47.4) |
| | Ranibizumab [c] | 22 (37.9) |
| | Aflibercept [c] | 36 (62.1) |
| 24 months | Eyes | 17 |
| | Baseline BCVA, ETDRS letters [a] | 56.3 (26.0) |
| | Final BCVA, ETDRS letters [a] | 64.0 (21.4) |
| | BCVA change, ETDRS letters [b] | +7.7 (-2.8; +18.2) |
| | Baseline CST, μm [a] | 464.1 (226.4) |
| | Final CST, μm [a] | 338.6 (169.5) |
| | CST change, μm [b] | -125.5 (-198.0; -53.0) |
| | Visits [d] | 23.0 (18.0; 27.0) |
| | Injections [d] | 11.0 (8.0; 15.0) |
| | Treatment interval, days [d] | 48.6 (36.8; 66.6) |
| | Ranibizumab [c] | 8 (47.1) |
| | Aflibercept [c] | 9 (52.9) |

BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; CST: central subfield thickness
[a] mean (standard deviation)
[b] mean (95% confidence interval)
[c] number (%)
[d] median (interquartile ratio)

**Table 3** Visual and anatomical outcomes for eyes initiating treatment with ranibizumab or aflibercept and completing 1 or 2 years of follow-up.

| Time Point | Outcomes | Ranibizumab | Aflibercept |
|---|---|---|---|
| 12 months | Eyes | 22 | 36 |
| | Baseline BCVA, ETDRS letters [a] | 61.4 (18.5) | 52.8 (24.9) |
| | Final BCVA, ETDRS letters [a] | 62.5 (24.5) | 61.2 (20.9) |
| | BCVA change, ETDRS letters [b] | +1.1 (-4.9; +7.1) | +8.4 (+0.9; +15.8) |
| | Baseline CST, μm [a] | 434.3 (119.9) | 456.6 (183.6) |
| | Final CST, μm [a] | 330.9 (74.3) | 341.0 (119.4) |
| | CST change, μm [b] | -103.4 (-154.5; -52.3) | -115.6 (-181.3; -49.9) |
| 24 months | Eyes | 8 | 9 |
| | Baseline BCVA, ETDRS letters [a] | 59.4 (27.1) | 53.5 (26.2) |
| | Final BCVA, ETDRS letters [a] | 62.2 (26.1) | 65.6 (17.6) |
| | BCVA change, ETDRS letters [b] | +2.8 (-5.1; +10.6) | +12.1 (-8.3; +32.5) |
| | Baseline CST, μm [a] | 414.4 (139.4) | 502.7 (278.8) |
| | Final CST, μm [a] | 266.1 (51.9) | 394.2 (218.0) |
| | CST change, μm [b] | -148.3 (-253.3; -43.3) | -107.8 (-227.4; -11.9) |

BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; CST: central subfield thickness; μm: micrometers
[a] mean (standard deviation)
[b] mean (95% confidence interval)

**Table 4** Adverse events in all eyes (n = 58) over their entire follow-up duration.

| Safety outcome | |
|---|---|
| Adverse events, n (%) | |
| Endophthalmitis | 0 (0.0) |
| Pre-retinal vitreous haemorrhage | 1 (1.7) |
| Retinal detachment | 0 (0.0) |
| Rubeosis | 0 (0.0) |
| Laser trabeculoplasty | 0 (0.0) |
| Incisional glaucoma surgery | 0 (0.0) |
| Starts new glaucoma medication | 0 (0.0) |
| Procedures, n (%) | |
| Cataract extraction | 10 (17.2) |
| Pars plana vitrectomy | 5 (8.6) |

## References


[1] Institut de Veille Sanitaire InVS. Le poids du diabète en France en 2016. Synthèse épidémiologique n.d. http://invs.santepubliquefrance.fr/Publications-et-outils/Rapports-et-syntheses/Maladies-chroniques-et-traumatismes/2018/Le-poids-du-diabete-en-France-en-2016.-Synthese-epidemiologique.

[2] Yau JWY, 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.

[3] Bertelsen G, Peto T, Lindekleiv H, Schirmer H, Solbu MD, Toft I, et al. Tromsø eye study: prevalence and risk factors of diabetic retinopathy. Acta Ophthalmol 2013;91:716–21.

[4] Varma R, Bressler NM, Doan QV, Gleeson M, Danese M, Bower JK, et al. Prevalence of and risk factors for diabetic macular edema in the United States. JAMA Ophthalmol 2014;132:1334–40.

[5] Fenwick EK, Pesudovs K, Khadka J, Dirani M, Rees G, Wong TY, et al. The impact of diabetic retinopathy on quality of life: qualitative findings from an item bank development project. Qual Life Res 2012;21:1771–82.

[6] Kiire CA, Porta M, Chong V. Medical management for the prevention and treatment of diabetic macular edema. Surv Ophthalmol 2013;58:459–65.

[7] Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, et al. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica 2017;237:185–222.

[8] 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.

[9] Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, et al. One-year outcomes of the Da Vinci study of VEGF Trap-Eye in eyes with diabetic macular edema. Ophthalmology 2012;119:1658–65.

[10] Fight Retinal Blindness - Save Sight Registries n.d. http://savesightregistries.org/registries/modules/fight-retinal-blindness/.

[11] Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol 1985;103:1796–806.

[12] 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.

[13] 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.

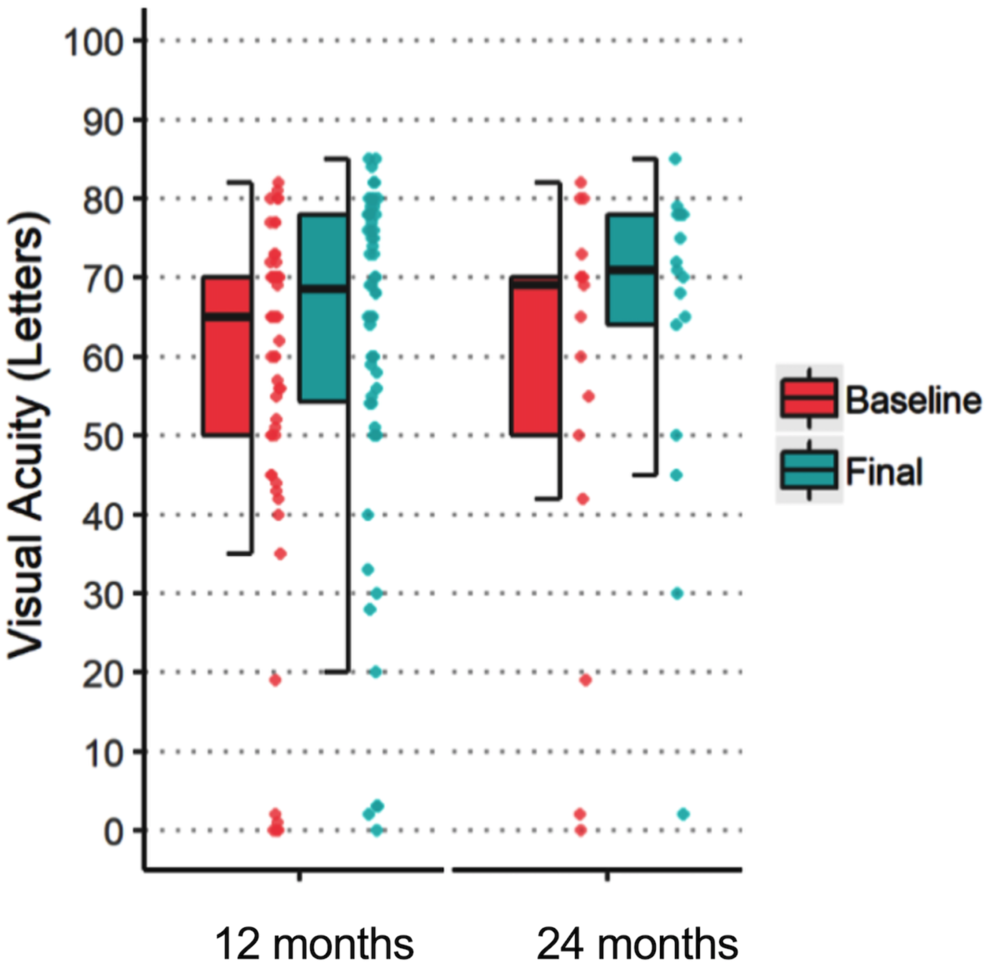
[14] Ashraf M, Souka A, Adelman R. Predicting outcomes to anti-vascular endothelial growth factor (VEGF) therapy in diabetic macular oedema: a review of the literature. Br J Ophthalmol 2016;100:1596–604.

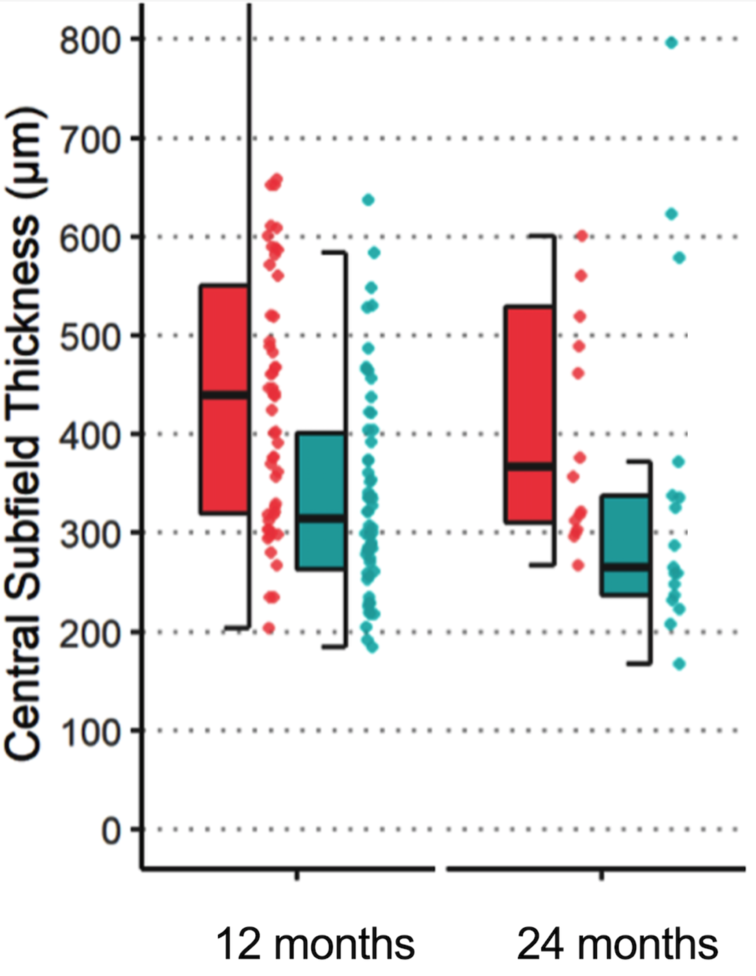
[15] Stefanickova J, Cunha-Vaz J, Ulbig M, Pearce I, Fernández-Vega Sanz A, Theodossiadis P, et al. A non-interventional study to monitor patients with diabetic macular oedema starting treatment with ranibizumab (POLARIS). Acta Ophthalmol

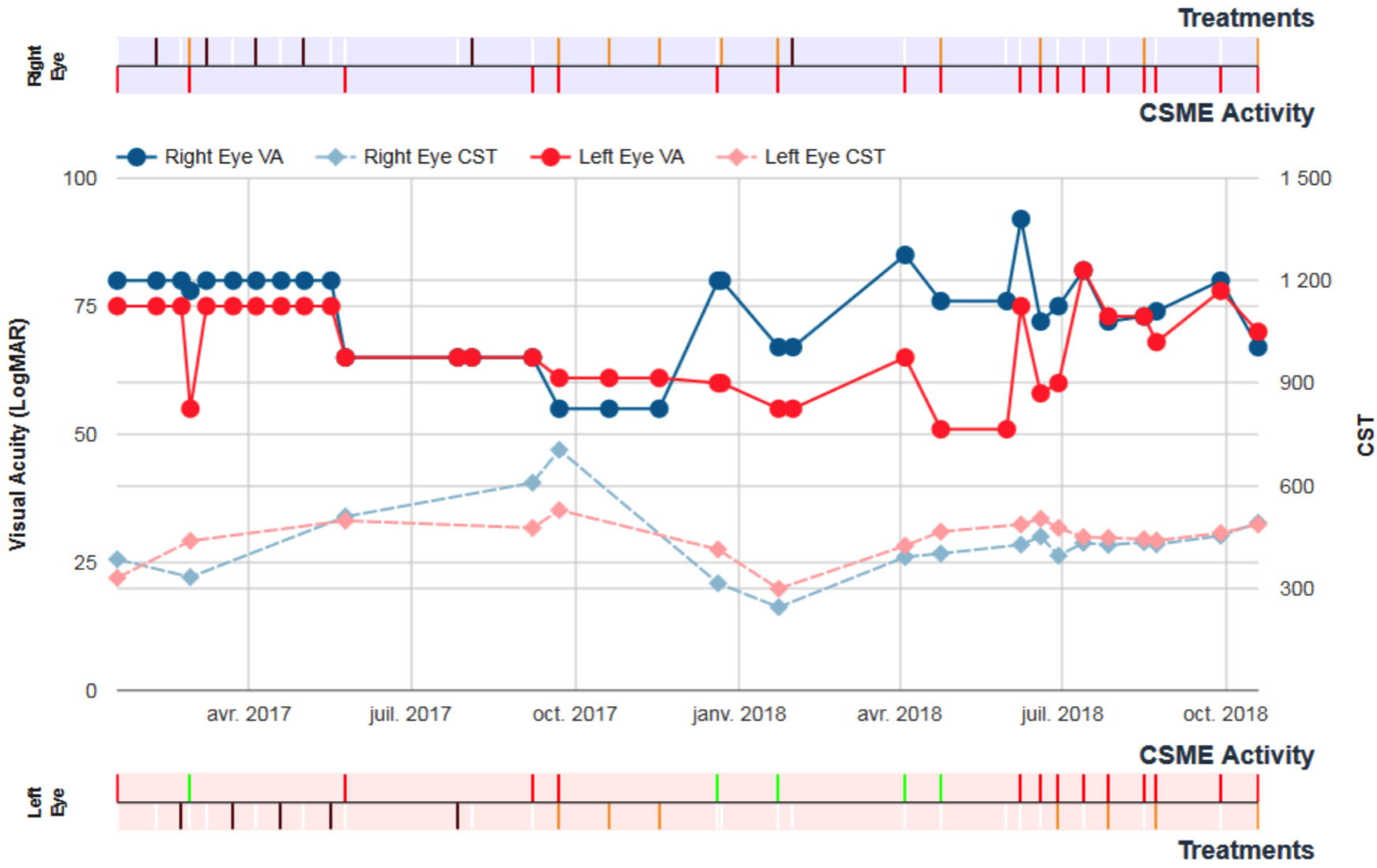
2018;96:e942–9.
[16] Ziemssen F, Wachtlin J, Kuehlewein L, Gamulescu M-A, Bertelmann T, Feucht N, et al. Intravitreal ranibizumab therapy for diabetic macular edema in routine practice: two-year real-life data from a non-interventional, multicenter study in Germany. Diabetes Ther 2018;9:2271–89.
[17] Best A-L, Fajnkuchen F, Nghiem-Buffet S, Grenet T, Quentel G, Delahaye-Mazza C, et al. Treatment efficacy and compliance in patients with diabetic macular edema treated with ranibizumab in a real-life setting. J Ophthalmol 2018;2018.
[18] Hodzic-Hadzibegovic D, Sander BA, Monberg TJ, Larsen M, Lund-Andersen H. Diabetic macular oedema treated with intravitreal anti-vascular endothelial growth factor - 2-4 years follow-up of visual acuity and retinal thickness in 566 patients following Danish national guidelines. Acta Ophthalmol 2018;96:267–78.
[19] Maggio E, Sartore M, Attanasio M, Maraone G, Guerriero M, Polito A, et al. Anti-vascular endothelial growth factor treatment for diabetic macular edema in a real-world clinical setting. Am J Ophthalmol 2018;195:209–22.
[20] Schmid MK, Reich O, Faes L, Boehni SC, Bittner M, Howell JP, et al. Comparison of outcomes and costs of ranibizumab and aflibercept treatment in real-life. PLoS ONE 2015;10:e0135050.
[21] Prünte C, Fajnkuchen F, Mahmood S, Ricci F, Hatz K, Studnička 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.
[22] Payne JF, Wykoff CC, Clark WL, Bruce BB, Boyer DS, Brown DM, et al. Randomized trial of treat and extend ranibizumab with and without navigated laser versus monthly dosing for diabetic macular edema: TREX-DME 2-year outcomes. Am J Ophthalmol 2019;202:91–9.
[23] Ebneter A, Waldmeier D, Zysset-Burri DC, Wolf S, Zinkernagel MS. Comparison of two individualized treatment regimens with ranibizumab for diabetic macular edema. Graefes Arch Clin Exp Ophthalmol 2017;255:549–55.
[24] Bégaud B, Polton D. Les données de vie réelle, un enjeu majeur pour la qualité des soins et la régulation du système de santé n.d.:105.

**Conflits d'intérêt :**

**M. T.** Aucun conflit d'intérêt
**C. M.** Aucun conflit d'intérêt
**C.C.-G.** Essais cliniques : Allergan, Bayer, Novartis et Roche
**A.-M. B.** Aucun conflit d'intérêt
**P. N.** Aucun conflit d'intérêt


Visual Acuity (Letters)
100
90
80
70
60
50
40
30
20
10
0
12 months
24 months
Baseline
Final


Central Subfield Thickness (µm)
800
700
600
500
400
300
200
100
0
12 months
24 months




**CSME Activity**

- Centre-involving CSME
- Non centre-involving CSME
- No CSME

**Eye Treatment Legend**

- Anti-vegf - eylea
- No treatment
- Pan retinal laser



VA: visual acuity
CST: Central subfield thickness
CSME: Clinically significant diabetic macular edema