Optimal Dose and Cost-effectiveness of Ranibizumab Treatment of Diabetic Macular Oedema

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A key treatment for diabetic macular oedema (DMO) is ranibizumab (Lucentis®, Genentech, California, US), which is approved at differing doses: 0.5 mg/month in Europe and 0.3 mg/month in the US. The relative efficacy and safety of these doses, however, is a controversial issue. A wide-ranging literature search was conducted to examine the evidence supporting these doses. The searches identified only four studies that evaluated the 0.3 mg ranibizumab dose, in which best-corrected visual acuity (BCVA) improvements ranged from +5.7 to +12.8 letters during treatment. The searches also identified 12 key studies that evaluated the 0.5 mg dose of ranibizumab, in which BCVA improvement ranged from +6.1 to +10.3 letters. The pivotal RIDE and RISE studies (n=382 and 377) were the only direct comparisons of the 0.3 mg and 0.5 mg ranibizumab doses and placebo. A pooled analysis of these studies showed that improvements in BCVA were numerically higher for the 0.3 mg-treated groups than for the 0.5 mg-treated groups at 24 and 36 months. Patients who were initially treated with sham injections and switched to ranibizumab did not match the improvements in those treated from the start. There was also little difference in central retinal thickness reduction between the two doses (261.8 and 261.2 µm versus 266.7 and 269.1 µm). Ranibizumab was well tolerated, adverse events occurred at similar frequencies in all groups, with a slightly greater incidence of stroke for the 0.5 mg dose. Analysis of RIDE and RISE also showed that ranibizumab is cost-effective. Overall, the data indicate that the 0.3 mg dose of ranibizumab is generally as effective as the 0.5 mg dose in DMO treatment.

Keywords

Ranibizumab, diabetic macular oedema, cost-effectiveness

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Diabetic macular oedema (DMO) is an increasingly serious healthcare issue and a leading cause of blindness worldwide.[1] Of the estimated 415 million people with diabetes globally, 7–12% have signs of DMO and 1–3% have visual impairment as a result.[2,3] This burden affects populations in all territories and is likely to increase substantially when the prevalence of diabetes burgeons to a predicted 642 million by 2040.[2–4] The availability of effective and tolerable treatments for the management of DMO is therefore critical in tackling a potential epidemic of blindness and visual impairment. Several treatments are available for DMO, including laser photocoagulation, intravitreal corticosteroids and anti-vascular endothelial growth factor (VEGF) agents. Prominent among the anti-VEGF agents is ranibizumab (Lucentis®, Genentech, California, US), which has an extensive body of clinical trial data supporting its efficacy and tolerability in DMO, and on which its approval by the US Food and Drug Administration and the European medicines Agency for use in this indication is based.[5–10] This monoclonal antibody (MAb) treatment has been used successfully as monotherapy and in combination with laser photocoagulation and with other treatments.[11–19] Manufacturing biological therapies, including MAbs, is an expensive process and their generally high cost has the potential to restrict usage in many territories, especially where healthcare resources are limited.[20–22] Reducing the dose of MAbs could lower this cost, provided that efficacy is not compromised markedly. Currently the licensed dose for ranibizumab in DMO in Europe is 0.5 mg/month as an intravitreal injection. In the US, however, the licensed dose is 0.3 mg/month due to concerns of cardiovascular risks in diabetic patients. This article reports the findings of literature searches of clinical studies that investigated the comparative efficacy and safety and cost-effectiveness of the 0.5 mg dose of ranibizumab in DMO compared with the lower 0.3 mg dose. These searches aimed to identify if there was superior efficacy in terms of visual acuity (VA) and central retinal thickness (CRT) or safety for either dose level in DMO treatment and whether the lower dose could be used as an alternative in many cases and thereby reduce costs.

Literature search methods and results

Combined searches were made in BIOSIS Previews®, British Library Inside Conferences, Embase®, Embase® Alerts and MEDLINE®, with no date restriction. Title and abstract terms searched for included MeSH terms for clinical studies in DMO, or diabetic retinopathy restricted to ranibizumab and 0.5 mg or 0.3 mg. In total, 157 unique references were identified. After removal of irrelevant articles and duplicate reports of the same studies, 47 relevant studies were identified. Of these, four studies included groups given only 0.3 mg ranibizumab as a comparator or single therapy,

Table 1: Non dose-comparison studies that assessed 0.3 mg doses of ranibizumab in the treatment of diabetic macular oedema

Reference	Design	Number of patients	Treatments	Study outcomes
Campochiaro et al., 2016[23]	Phase IIa, randomised, placebo- and sham injection-controlled, double-masked	144	1.AKB-9778 alone 15 mg + monthly sham inj; 2. subcut AKB-9778 15 mg BID + monthly RBZ 0.3 mg; 3. RBZ 0.3 mg monotherapy: subcut placebo injections BID + monthly RBZ 0.3 mg	At Week 12 Mean change from baseline BCVA (letters): 6.3±1.3 in combination group, 5.7±1.2 in the RBZ monotherapy group, and 1.5±1.2 in the AKB-9778 monotherapy group. Proportions of eyes gaining ≥10 or ≥15 letters were: 8.7% and 4.3%, in the AKB-9778 monotherapy group, 29.8% and 17.0%, in the RBZ monotherapy group, and 35.4% and 20.8%, in the combination group. Mean changes in CST at Week 12 were 6.2±13.0 µm for AKB-9778 alone –164.4±24.2 µm for AKB-9778 + RBZ and –110.4±17.2 µm for RBZ alone.
Wells et al., 2016[25] DRCRN	Randomised clinical trial	666	1. AFB 2.0 mg; 2. BEV 1.25 mg (repackaged (compounded) bevacizumab 3. RBZ 0.3 mg	At 2 years for AFB 2.0 mg, BEV 1.25 mg and RBZ 0.3 mg, mean VA improved overall by 12.8, 10.0 and 12.3 letters. For pts with worse baseline VA (20/50 to 20/320), mean improvement was 18.1, 13.3 and 16.1 letters (AFB versus BEV, p=0.02; AFB versus RBZ p=0.18; RBZ versus BEV, p=0.18). With better baseline VA (20/32 to 20/40), mean improvement was 7.8, 6.8 and 8.6 letters (p>0.10, for pairwise comparisons).
Wiley et al., 2016[26]	Randomised, double-masked, 36-week, 3-period crossover clinical trial	56	1. BEV 1.25 mg; 2. RBZ 0.3 mg	3-month estimated mean improvement in VA was 5.3 letters for BEV and 6.6 letters for RBZ (difference, 1.3 letters; p=0.039). Estimated change in CRT was -89 µm for BEV and -137 µm for RBZ (difference, 48 µm; p<0.001). There was a statistically significant but small relative clinical benefit of RBZ vs BEV for treatment of DMO in a small sample size.
Cuilla et al., 2015[24]	Retrospective chart review	33 eyes of 22 pts	RBZ 0.3 mg	Mean BCVA before initial RBZ was 20/110 and mean CRT was 384 µm. After seven visits over an average of 48 weeks, and an average of 6 RBZ inj, mean BCVA was 20/90 and the mean CRT improved to 335 µm.

AFB = aflibercept; BCVA = best corrected visual acuity; BEV = bevacizumab; BID = twice daily; CRT = central retinal thickness; CST = central subfield thickness; pts = patients; RBZ = ranibizumab; VA = visual acuity.

28 studies included groups given only 0.5 mg ranibizumab and only two studies directly compared the 0.3 mg and 0.5 mg ranibizumab doses. The designs, patient dispositions and findings of these categories are summarised in *Tables 1, 2* and *3* (only completed studies with >40 patients for the ranibizumab 0.5 mg dose are tabulated).

The effect of different ranibizumab dosing regimens, the efficacy of ranibizumab compared with other treatments for DMO and in combination with other agents is outside the scope of this article.

Studies including only a 0.3 mg ranibizumab dose group – in diabetic macular oedema

There have been few studies that evaluated the 0.3 mg ranibizumab dose as a discrete group in the treatment of DMO (see *Table 1*). The four relevant studies ranged from 22 to 666 patients in size (mean 222 patients) and treatment durations varying from three months to two years.[23–26] In three of the studies, ranibizumab monotherapy was a comparator against alflibercept, or bevacizumab or compared or in combination with AKB-9778 (a small-molecule competitive inhibitor of vascular endothelial-protein tyrosine phosphatase).[23,25,26] One study was a retrospective chart review.[24] Treatment durations were from one month to two years, during which best-correct visual acuity (BCVA) improved from +5.7 to +12.8 letters and improvements in VA. In one study there were no significant differences at the end of two years in VA for ranibizumab 0.3 mg compared with aflibercept 2.0 mg or bevacizumab 1.25 mg (p=0.18 for both) for patients with worse baseline VA (20/50 to 20/320).[25] Results were similar in patients with better baseline VA (20/32 to 20/40). In another study ranibizumab 0.3 mg was significantly better than bevacizumab 1.25 mg in terms of VA -6.6 letters versus 5.3 letters (p=0.039).[26] Reductions in CRT were -89 and -137 µm during treatment for bevacizumab and ranibizumab, respectively (p=<0.001). The ranibizumab treatment in these studies was well tolerated with no new adverse events profiles, i.e., these profiles being similar to those reported for the phase III studies.[27,28]

These studies had varying designs, study endpoints, patient populations and treatment durations, making direct comparisons difficult. However, a strong overall message that emerges from these studies is that 0.3 mg dose of ranibizumab is effective and has potential as a clinical treatment in DMO which was similar to or superior to that of some other treatments.

Studies including a 0.5 mg ranibizumab dose group (not 0.3 mg) in diabetic macular oedema

A greater body of clinical study evidence supports the use of the 0.5 mg dose of ranibizumab than the 0.3 mg dose in DMO treatment. Twelve key studies (mainly >100 patients) that investigated patients treated with ranibizumab 0.5 mg dose in DMO as single or comparator groups are summarised in *Table 2*.[11,15,16,18,29–35] Patient populations among this group ranged from 41 to >600, with a mean of 249 patients. Treatment durations varied from five months to five years. The mean improvement in VA ranged from +6.1 to +10.3 letters (BCVA) with some studies reporting 46–60.8% of patients showing a ≥10-letter improvement during treatment. Reductions in CRT (where reported) ranged from -118.7 µm to -214.0 µm. In four of these studies (READ-2, RESPOND, RETAIN and REVEAL – see below for definitions of study names), ranibizumab 0.5 mg monotherapy was compared with either laser photocoagulation alone or a combination of ranibizumab 0.5 mg and laser treatment.[11,16,33,35] In each case, laser treatment alone produced poorer improvements in VA and CRT than ranibizumab 0.5 mg. Combinations of ranibizumab 0.5 mg and laser treatment produced no better or poorer efficacy than ranibizumab 0.5 mg alone. In the DRCRNet study, patients with DMO received monthly ranibizumab and either laser treatment given promptly or deferred for ≥24 weeks.[15] After 2 years, there was vision loss of ≥10 letters in 9% and 8% of patients, in the prompt and deferred laser treatment groups, respectively, and improvements of ≥10 letters in 46% and 58%, respectively. A total of 56% in the deferred

Table 2: Key non dose-comparison studies (>40 patients) that assessed 0.5 mg and greater doses of ranibizumab in the treatment of diabetic macular oedema

Study name and reference	Design	Number of patients	Treatments	Study outcomes
ADMOR –SE Ghanchi et al., 2016[30]	Real-world study single group in Asia	51 eyes of 41 pts	RBZ 0.5 mg	12-month: mean ETDRS VA increased from 55.3±13.4 letters to 63.8±15.2 letters for all eyes. 70.6% eyes gained 5 or more letters acuity and 17.6% eyes gained 15 letters or more. Mean CMT decreased from 532±129 to 318±136 µm. Eyes that had received previous laser treatments had a mean letter gain of 9.2 letters, compared with 8.5 for all eyes at 12 months. RBZ 0.5 mg is safe and effective at reversing vision loss due to DMO in pts of South Asian origin at 12 months.
DRCRN Elman et al., 2015[15]	Phase III Multicentre, randomised clinical trial	235	1. RBZ 0.5 mg + prompt laser; 2. RBZ 0.5 mg + deferred laser	Mean change in VA score from baseline to 5-year: +7.2 letters in the prompt laser group versus +9.8 letters in deferred laser group (mean difference, -2.6 letters; p=0.09). At 5-years in the prompt versus deferred laser groups, there was visual loss of ≥10 letters in 9% versus 8%, an improvement of ≥10 letters in 46% versus 58%, and an improvement of ≥15 letters in 27% versus 38% of participants.
PRIDE Menchini et al., 2015[32]	Phase IIIb Open-label, prospective, study.	>600 pts 515 completers	RBZ 0.5 mg	RBZ improved/maintained VA (Snellen [20/value]/decimal scores) in both unilateral (up to -16.7/1.5) and bilateral patients (up to -23.6/1.2) at Month 5, with a mean of 4.15 and 4.40 injections, respectively. No difference observed in the VA outcomes and treatment exposure between unilateral/bilateral patients.
READ-2 Nguyen et al., 2009[33]	Phase II Prospective, randomised, interventional, multicentre clinical trial	126	1:1:1 randomisation: 1. 0.5 mg RBZ at baseline and months 1, 3, and 5 (group 1, 42 pts); 2. laser photocoagulation at baseline and month 3 if needed (group 2, 42 pts); 3. combinations of RBZ 0.5 mg and focal/grid laser at baseline and month 3 (group 3, 42 pts)	For the 33 pts in group 1, 34 pts in group 2, and 34 pts in group 3 at 24 months, mean improvement in BCVA was 7.4, 0.5 and 3.8 letters at the 6-month primary end point, versus 7.7, 5.1 and 6.8 letters and the percentage of pts who gained 3 lines or more of BCVA was 21, 0, and 6 at month 6, versus 24, 18 and 26. RBZ provided benefit for patients with DMO for at least 2 years, and when combined with focal or grid laser treatments, the amount of residual oedema was reduced, as were the frequency of injections needed to control it.
READ-3 Do et al., 2015[29]	Phase II Randomised, controlled, multicentre clinical trial	152	0.5 mg (n=77) or 2.0 mg (n=75) RBZ	At month 6, the mean improvement from baseline BCVA was +9.43 letters in the 0.5 mg RBZ group and +7.01 letters in the 2.0 mg RBZ group (p=0.161). Mean CFT was reduced by 168.58 µm in the 0.5 mg RBZ group and by 159.70 µm in the 2.0 mg RBZ group (p=0.708).
REEF Dhoot et al., 2015[36]	12-month prospective, nonrandomised, multicentre study	43	3 monthly RBZ 0.5 mg injections. At month 3, patients with residual macular oedema were switched to three monthly injections of RBZ 2.0 mg (recruited patients with poor response to BEV)	Mean VA improved by +6.4 letters at month 3 and +8.8 letters at month 6. Mean CST decreased by -113 µm at month 3 and -165 µm at month. Ranibizumab 0.5 mg or 2.0 mg may improve visual and anatomic outcomes in patients with DMO with minimal or no response to BEV. Increased dosage of RBZ (2.0 mg) may provide additional benefit over RBZ 0.5 mg in some patients. However, 2.0 mg RBZ is not currently commercially licensed or available.
RELIGHT Pearce et al., 2015[34]	Phase IIIb, 18-month, prospective, open-label, multicentre, single-arm study	109	3 initial monthly RBZ 0.5 mg inj (day 0 to month 2), followed by BCVA and OCT-guided re-treatment with monthly (months 3-5) and subsequent bimonthly follow-up (months 6-18). Laser was allowed after month 6	Mean baseline BCVA: 62.9 letters. Mean change in BCVA from baseline to month 6: +6.6 letters, after start of bimonthly treatment the mean change in BCVA at month 12 was +4.8 letters (p<0.001) and +6.5 letters at month 18. Proportions of participants gaining ≥10 and ≥15 letters: 24.8% and 13.8% at month 12 and 34.9% and 19.3% at month 18. BCVA gain achieved in the initial 6-month treatment period was maintained with an additional 12 months of bimonthly ranibizumab PRN treatment.
RESOLVE Massin et al., 2010[31]	Phase II 12-month, multicentre, sham-controlled, double-masked study	151	1:1:1 randomisation: 1. RBZ 0.3 mg; 2. RBZ 0.5 mg; 3. Sham inj RBZ 0.3 and 0.5 mg results were pooled and not directly compared	At 12 months, BCVA improved from baseline by 10.3±9.1 letters with RBZ and declined by 1.4±14.2 letters with sham (p<0.0001). Mean CRT reduction was 194.2±135.1 µm with RBZ and 48.4±153.4 µm with sham (p<0.0001). Gain of ≥10 letters BCVA from baseline occurred in 60.8% of RBZ and 18.4% of sham eyes (p<0.0001) R is effective in improving BCVA and is well tolerated in DMO.
RESPOND Berger et al., 2015[11]	Phase III 12-month, multicentre, open-label, parallel-group, randomised, active-control study	220	1:1:1 randomisation: 1. RBZ 0.5 mg monotherapy: n=75; 2. RBZ 0.5 mg + laser: n=73; 3. laser monotherapy: n=72	At 12 months, significant (p<0.001) mean BCVA improvements were observed for both RBZ monotherapy (+8.9 letters) and the RBZ + laser (+8.2 [95% CI 6.0-10.4] letters) groups versus laser monotherapy group (+0.3 letters). A better response for CRT improvement, BCVA letter gain, and VFQ-25 was observed in both RBZ groups versus laser monotherapy.

Table 2: Cont.

Study name and reference	Design	Number of patients	Treatments	Study outcomes
RESTORE Mitchell et al., 2011[18]	Phase III 12-month, randomised, double-masked, multicentre, laser-controlled study.	345	1. RBZ 0.5 mg + sham laser (n=116); 2. RBZ 0.5 mg + laser (n=118); 3. Sham inj + laser (n=111)	RBZ alone and combined with laser were superior to laser monotherapy in improving mean average change in BCVA letter score from baseline to month 1 through 12 (+6.1 and +5.9 versus +0.8; both p<0.0001). At month 12, a significantly greater proportion of patients had a BCVA letter score ≥15 and BCVA letter score level >73 (20/40 Snellen equivalent) with RBZ (22.6% and 53%, respectively) and RBZ + laser (22.9% and 44.9%) versus laser (8.2% and 23.6%). The mean CRT was significantly reduced from baseline with RBZ (-118.7 µm) and RBZ + laser (-128.3 µm) versus laser (-61.3 µm; both p<0.001).
RETAIN Prunte et al., 2016[35]	Phase III 24-month single-masked study	372	1:1:1 randomisation to: 1. RBZ 0.5mg T&E + laser (n=121); 2.RBZ 0.5 mg T&E (n=128); 3. RBZ 0.5 mg PRN (control; n=123)	Mean BCVA change at month 24 was similar across groups (+8.3, +6.5 and +8.1 letters). The mean number of injections was 12.4 and 12.8 in the T&E +l aser and T&E groups and 10.7 in the PRN group. The T&E regimens showed 46% reduction in clinic visits. Over 70% of patients maintained their BCVA, with treatment intervals of ≥2 months over 24 months. T&E is a feasible treatment option for patients with DMO, with a potential to reduce treatment burden.
REVEAL Ishibashi et al., 2015[16]	Phase III 12-month, randomised, double-masked, multicentre, laser-controlled, study	396	1. RBZ 0.5 mg + sham laser (n= 33); 2. RBZ 0.5 mg + active laser (n=132); 3. Sham inj + active laser (n=131)	At month 12, greater proportion of patients gained ≥15 letters with RBZ and RBZ + laser versus laser (18.8% and 17.8% versus 7.8%). Mean CRT reduced significantly from baseline to month 12 with RBZ (-134.6 µm) and RBZ + laser (-171.8 µm) versus laser (-57.2 µm).

AFB = aflibercept; BCVA = best-corrected visual acuity; BEV = bevacizumab; CI = confidence interval; CFV = central foveal thickness; CMT =- central macular thickness; CRT = central retinal thickness; CST = central subfield thickness; DMO = diabetic macular oedema; ETDRS = Easrly Treatment Diabetic Retinopathy Study (scale); inj = intravitreal injection; OCT = optical coherence tomography; PRN = pro re nata (therapy as needed); pts = patients; RBZ = ranibizumab; T&E = treat and extend; VA = visual acuity; VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25.

treatment group received no laser treatment at all over 5 years. This suggested that prompt laser treatment was not advantageous over deferred treatment and that for many patients, ranibizumab 0.5 mg is effective as monotherapy.

In the READ-3 study, patients with DMO were treated with either ranibizumab 0.5 mg or 2.0 mg. Improvements in BCVA were numerically lower with the higher dose (+9.43 versus +7.01 letters) but there was no statistically significant difference.[29] The reduction in CRT was also lower with the higher dose. In the REEF study, patients with DMO were treated initially with ranibizumab 0.5 mg for three months and those with residual DMO were switched to ranibizumab 2.0 mg.[36] VA had improved by +6.4 letters at month three and by +8.8 letters after month six. The study authors concluded that the 2.0 mg dose could provide additional benefit in some patients.

The RESOLVE study included groups of patients with DMO who were initially randomized to ranibizumab 0.3 mg and 0.5 mg, and sham injections but after month one, dose-doubling was permitted.[31] This meant that there was overlap in the doses received by the two active treatment groups. In the analysis, the results of these groups were therefore pooled and compared with sham treatment; a direct comparison of the 0.3 mg and 0.5 mg results was thus not possible.

In all of these trials using the 0.5 mg dose, ranibizumab was considered safe and well tolerated. The occurrence and type of adverse events and serious adverse events were similar to patients receiving sham injections. Adverse events that were reported at low frequency (<3%) with ranibizumab over 12 months included conjunctival haemorrhage, eye pain, nasopharyngitis, hypertension, arterial thromboembolic events such as myocardial infarction. Serious ocular adverse events were reported in 1.8% of patients and included vitreous haemorrhage, retinal ischaemia, retinal artery occlusion and endophthalmitis.[27]

As with the 0.3 mg ranibizumab dose studies, the designs, treatment durations and endpoints were variable in the 0.5 mg dose studies but they showed consistent efficacy and tolerability in differing patient groups and locations. Overall, the study results for 0.3 mg or 0.5 mg intravitreal ranibizumab show similar efficacy for both doses.

Studies directly comparing 0.3 mg and 0.5 mg ranibizumab doses in diabetic macular oedema

Only two large-scale studies have directly compared the ranibizumab 0.3 mg and 0.5 mg doses in DMO.[27,28,37] These were the Phase III RIDE and RISE studies that were run from 2007–2012 and involved 759 adults with DMO having BCVA 20/40 – 20/320 and CRT ≥275 µm. (see *Table 3*). The study designs were identical; participants were randomised 1:1:1 to monthly ranibizumab 0.3 mg or 0.5 mg or sham injections for 24 months. After that, the remaining patients could opt to enter the open-label extension in which sham-treated patients could switch to 0.5 mg ranibizumab. After 36 months, all patients were switched to pro re nata (PRN)-based treatment for a maximum of 2 years.

For the primary endpoint, the proportions of patients in both studies gaining ≥15 letters BCVA, at 24 and 36 months were similar in the ranibizumab 0.3 mg- and 0.5 mg-treated groups but markedly higher than in sham-treated patients. Indeed, the pooled changes in BCVA in the 0.3 mg treated groups was numerically higher than 0.5 mg at both time points (see *Figure 1*).[27] Plots of changes in the proportions gaining ≥15 letters and changes in proportions with <15 letter loss over 36 months also show similar benefits from patients receiving either ranibizumab doses compared with those who received sham treatment (see *Figure 2*). During months 24–36, when the previously sham-treated patients were switched to ranibizumab 0.5 mg, there was an improvement in VA, but this did not match the improvements seen in the groups treated with either 0.3 mg or 0.5 mg ranibizumab throughout.[27] This indicated that delaying ranibizumab treatment has a

Table 3: Studies directly comparing 0.3 mg with 0.5 mg doses of ranibizumab in the treatment of diabetic macular oedema

Study and reference	Design	Number of patients in analysis	Treatments	Study outcomes
RIDE Brown et al., 2013[28] Boyer et al., 2015[27]	Phase III, randomised, multicentre, double-masked, 3-year trial	382 at Month 24, 382 at Month 36, 112 at Month 48	Randomised 1:1:1 to monthly intravitreal injections*: 1. RBZ 0.3 mg; 2. RBZ 0.5 mg; 3. Sham	For 0.3 mg, 0.5 mg and sham (or sham/crossover for Month 48): • % gaining ≥15 ETDRS letters: Month 24: 33.6, 45.7, 12.3 Month 36: 36.8, 40.2, 19.2 Month 48: 48.7, 41.0, 17.6 • % with <15 letter loss from baseline at: Month 24: 98.4, 96.1, 91.5 Month 36: 96.8, 96.1, 92.3 Month 48: 97.4, 97.4, 94.1 • ETDRS letter change from baseline at Month 36: 10.6, 11.4, 4.7 • Mean change in CRT from baseline (μm) at Month 36: –261.8, –266.7, –213.2 • Mean change in CRT (μm) Month 36–48: 46.1, 44.1, 9.6
RISE Brown et al., 2013[28] Boyer et al., 2015[27]	Phase III, randomised, multicentre, double-masked, 3-year trial	377 at Month 24, 377 at Month 36, 166 at Month 48	Randomised 1:1:1 to monthly intravitreal injections*: 1. RBZ 0.3 mg; 2. RBZ 0.5 mg; 3. Sham	For 0.3 mg, 0.5 mg and sham (or sham/crossover for Month 48): • % gaining ≥15 ETDRS letters Month 24: 44.8, 39.2, 18.1 Month 36: 51.3, 41.6, 22.0 Month 48: 50.0, 48.2, 22.9 • % with <15 letter loss from baseline at: Month 24: 97.6, 97.6, 89.8 Month 36: 99.2, 97.6, 91.3 Month 48: 100, 100, 97.9 • ETDRS letter change from baseline at Month 36: 14.2, 11.0, 4.3 • Mean change in CRT from baseline (μm) at Month 36: –261.2, –269.1, –200.1 • Mean change in CRT (μm) Month 36–48: 23.3, 4.2, 29.6
Overall findings of RIDE and RISE studies	There were notable gains in vision and reductions in CRT for monthly treatment with either RBZ 0.3 mg or 0.5 mg doses during the 24-month randomised treatment period and these were maintained during the open-label phase. These gains were also maintained during the PRN phase when treatment frequency was markedly reduced – some patients required no further treatment. Patients who were originally randomised to sham injections and whose RBZ treatment was deferred by 24 months did not show the same amount of vision gains as those who received it from baseline. The safety profile of RBZ was consistent with that reported for the other single-dose studies.			

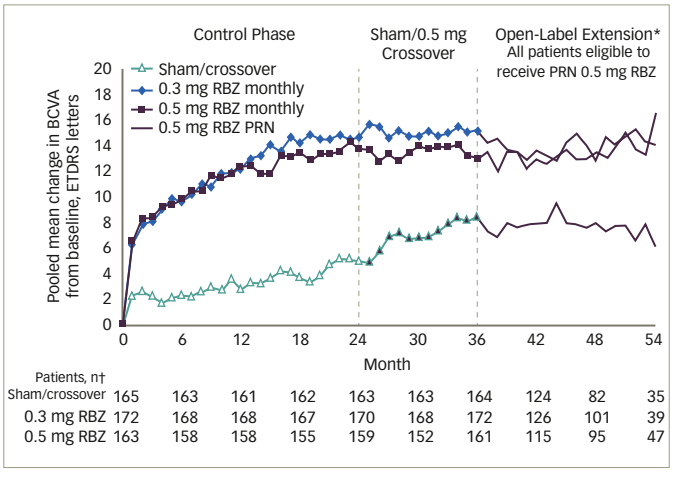
** The duration of randomised treatment in three groups was 24 months at which point sham-treated patients who remained in the study could choose to receive monthly, open-label RBZ 0.5 mg for 12 months and patients receiving monthly RBZ 0.3 mg or 0.5 mg continued on the same treatment for a further 12 months. At 36 months' treatment for all groups was switched from monthly to a PRN basis for a further 2 years. This resulted in a maximum exposure to RBZ treatment of 5 years. CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study (scale); PRN = pro re nata (therapy as needed); RBZ = ranibizumab. See end of text for definitions of study names.*

negative impact that cannot be fully reversed. During months 36 to 54, PRN-based treatment generally maintained the improvements VA seen at Month 36 in all three groups.

There were similarly marked reductions in CRT in both the ranibizumab dose groups during controlled treatment up to 36 months and these were substantially greater than reductions in the sham-treated groups.[27,28] During months 36–48, however, when ranibizumab PRN treatment was instituted and patients received less intensive therapy, there was a trend towards slight retinal thickening (see *Table 3*). The proportions of patients showing improvements in diabetic retinopathy severity scores during controlled treatment and the open-label extension phase were similar in the ranibizumab 0.3 mg and 0.5 mg groups and greater than the sham/crossover groups. The efficacy of the ranibizumab 0.3 mg and 0.5 mg doses in terms of their effects on VA, disease severity, CRT and long-term outcomes was therefore generally similar in the RIDE and RISE studies but tended to show a more marked effect than in studies where these doses were used singly.

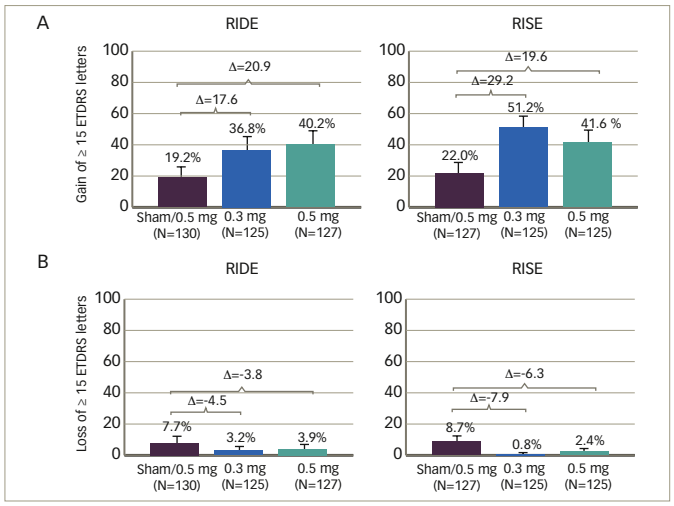
For safety and tolerability, during the sham-controlled treatment periods in the RIDE and RISE studies up to 24 months, the overall occurrence of ocular adverse events was similar in all groups (84.8–88.4%).[28] Events such as glaucoma (2.8%, 2.8% and 2.4% for 0.3 mg, 0.5 mg and sham/

Figure 1: Pooled mean change from baseline in best-corrected visual acuity among patients during the controlled and open label extension phases of the RIDE and RISE studies



*†ETDRS = Early Treatment Diabetic Retinopathy Study; PRN = pro re nata; RBZ = ranibizumab. *Data become unstable after month 54 because of the low number of patients at that point. †Treatment during core study. Reproduced from Boyer et al. 2015[27] under the Creative Commons Attribution-NonCommercial-No Derivatives License.*

Figure 2: Visual acuity outcomes at 36 months in the RISE and RIDE studies



ERDRS = Early Treatment Diabetic Retinopathy Study. Reproduced from Brown et al. 2015[28] under the Creative Commons Attribution-NonCommercial-No Derivatives License.

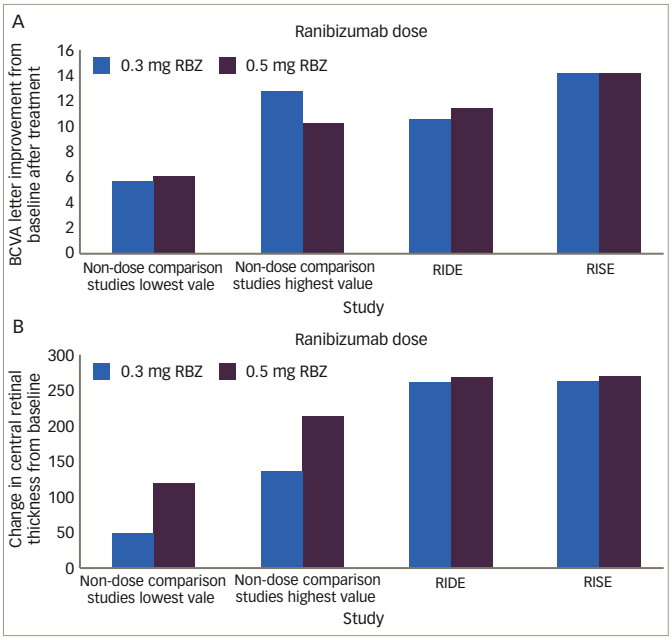
crossover groups, respectively) and increased intraocular pressure (17.6%, 16.4% and 6.8%, respectively) occurred with similar frequency at both doses. Serious ocular adverse events were generally more frequent with ranibizumab 0.5 mg than 0.3 mg including angle-closure glaucoma (0%, 0.4% and 0.4%), endophthalmitis (0.8%, 0.8% and 0%), cataract (0.45 and 0.8% and 0%) and vitreous haemorrhage (0%, 0.8% and 2.8%). This pattern was continued during months 24–36 and during the subsequent PRN-based treatment phase.

Arterial thrombotic events occurred at similar rates in the two ranibizumab groups, which were higher than the sham/crossover-treated group (10.8%, 10.4% and 7.2% for ranibizumab 0.3 mg, 0.5 mg and sham/crossover groups, respectively). Among these, myocardial infarction and stroke were slightly more frequent during ranibizumab treatment. Stroke was also more common with the 0.5 mg than the 0.3 mg dose (4.8% versus 2.0%). Overall, the safety and tolerability profiles of both ranibizumab doses were similar in the RIDE and RISE studies and did not differ markedly from that of single-dose studies summarised in the previous sections.

Cost-effectiveness of ranibizumab doses in diabetic macular oedema

A few studies have reported positive cost-effectiveness findings for the ranibizumab 0.3 mg or 0.5 mg doses. One example is a 14-year cost-utility analysis using data from the RIDE and RISE studies.[38] This study found that the 14-year incremental patient value gain for the 0.3 mg ranibizumab dose in DMO was 0.9981 quality-adjusted life year (QUALY). The direct cost for ranibizumab in one eye was determined to be US$30,116 and for two eyes was US$56,336. Savings from decreased depression, injury, skilled nursing facility admissions, nursing home admissions, and other vision-associated costs were estimated to be US$51,758, leaving an overall cost of US$4578. It was concluded that ranibizumab 0.3 mg confers considerable patient (human) value gain and accrues value to patients, public, insurers and society. A study in the UK, using findings from the RESTORE study, estimated that lifetime costs per patient in DMO treatment were £20,019 for ranibizumab 0.5 mg PRN, £22,930 for ranibizumab 0.5 mg treat and extend, based on 3-year treatment time-frame.[39] From these findings, ranibizumab 0.5 mg was considered cost-effective and compared favourably with other DMO therapies.

Figure 3: Comparison of efficacy between ranibizumab 0.3 mg and 0.5 mg doses in multiple diabetic macular oedema treatment studies



A: BCVA letter improvement from baseline; B: central retinal thickness reduction from baseline. BCVA = best corrected visual acuity; RBZ = ranibizumab. Source: Studies with no direct dose comparison: values ranges determined in present literature analysis. Information sourced from RISE and RIDE: Brown et al. 2013,[28] Boyer et al. 2015[27].

Discussion

Looking at the data from trials that used only one dose of ranibizumab, it is apparent that the ranges of VA improvement in terms of increased BCVA letters and proportions of patients with increased letter scores produced by the 0.3 mg and 0.5 mg doses overlapped so that their efficacy appears substantially similar. The range of decreases in CRT also overlapped but clearly greater reductions were seen with the 0.5 mg dose (see *Figure 3*). The studies that are discussed above varied in design, endpoints, treatment durations and study populations so it is difficult to draw consistent and reliable conclusions that can be compared. Nevertheless, across a wide range of these studies the efficacy of the two doses appears similar. Safety findings indicate good tolerability with ocular adverse events generally occurring at similar frequencies with ranibizumab to those of sham injections.

The RIDE and RISE trials provide a more reliable basis for comparing the 0.3 mg and 0.5 mg doses of ranibizumab over long treatment durations than those that evaluated only a single dose. The overall improvements in VA and in CRT were quite similar between the two doses in both trials but of greater magnitude than seen in other studies (see *Figure 3*). The reasons for this greater efficacy may have been a result of more intense therapy over longer durations in the RIDE and RISE studies. The gains in VA and CRT for both doses were maintained over three years of intensive monthly treatment and continued during the further 18 months of PRN treatment. There was some degree of retinal thickening during the PRN phase suggesting that this less frequent treatment regimen may be insufficient for some patients. Patients who received sham treatment initially and were switched at 24 months failed to achieve the gains indicating that some disease progression is irreversible and early initiation of treatment following DMO diagnosis is vital. The overall findings led the authors of long-term outcomes to conclude that 'in the pooled data from the RIDE and RISE trials efficacy was equivalent between the 0.3 mg and 0.5 mg doses'.[28]

The safety findings of all these trials indicate the generally favourable safety profiles and tolerability of both ranibizumab doses. Some ocular adverse events such as endophthalmitis, glaucoma and cataract may be expected with intravitreal injections but these were generally non-severe and few led to treatment discontinuation, particularly in the ranibizumab 0.3 mg group (0.4% and 1.2% for 0.3 mg and 0.5 mg, respectively at 36 months). In the RIDE and RISE studies ocular adverse events generally occurred at the same frequencies in ranibizumab and sham-treated patients. Among systemic events there was a slight increase in cardiovascular thrombotic events with ranibizumab including increased stroke risk. Since 40–50% of patients with DMO have bilateral DMO requiring simultaneous treatment[40] and that diabetic patients have an increased risk of mortality and cardiovascular disease,[41] the lower 0.3 mg dose of ranibizumab was considered more suitable than the 0.5 mg dose for use in DMO and was consequently licensed for this indication by the US Food and Drug Administration.[28]

Cost-effectiveness studies indicate that both ranibizumab doses improve quality of life and were considered by investigators to provide value when the cost of other treatments, welfare and the high financial impact of vision impairment to the patient are taken into account. However, the high cost of this treatment is still likely to limit or even prevent its use in many territories and in patients with inadequate healthcare insurance. Since the ranibizumab 0.3 mg dose appears to be equivalent to the 0.5 mg dose in terms of efficacy and has potential safety benefits, using the lower dose could be appropriate for many patients in Europe and elsewhere to reduce costs. This would make the treatment more accessible to a wider patient population with DMO. The 0.5 mg and higher ranibizumab doses could then be reserved for some patients including more severe or refractory cases as was suggested by the authors of the REEF study (see *Table 2*).[36] The ever-increasing prevalence of DMO is likely to drive demand for effective but lower-cost treatments that can stem a rising burden of vision loss worldwide. Using the lower 0.3 mg dose of ranibizumab across all territories could help satisfy this need. ❑

Definitions of study names:

ADMOR SE: South Asian diabetic macular oedema treated with ranibizumab; DRCRN: Diabetic Retinopathy Clinical Research Network; ETRDS: Early Treatment Diabetic Retinopathy Study; PRIDE: Multicenter 12 months clinical study to evaluate efficacy and safety of ranibizumab alone or in combination with laser photocoagulation vs. laser photocoagulation alone in proliferative diabetic retinopathy; READ-2: Ranibizumab for edema of the macula in diabetes-2; READ-3: Ranibizumab for edema of the macula in diabetes: protocol 3 with high dose; REEF: Ranibizumab 0.5mg and 2.0 mg to Treat Diabetic Macular Edema in Patients With Poor Response to Bevacizumab; RELIGHT: ranibizumab treatment of diabetic macular oedema with bimonthly monitoring after a phase of initial treatment; RESOLVE: Safety and efficacy of ranibizumab in diabetic macular edema with center involvement; RESPOND: Safety, efficacy and cost-efficacy of ranibizumab (monotherapy or combination with laser) in the treatment of diabetic macular edema; RESTORE: A 12 Month core study to assess the efficacy and safety of ranibizumab (intravitreal injections) in patients with visual impairment due to diabetic macular edema and a 24 month open-label extension study; RETAIN: Efficacy and safety of ranibizumab in two "treat and extend" treatment algorithms versus ranibizumab as needed in patients with macular edema and visual impairment secondary to diabetes mellitus; REVEAL: Efficacy and safety of ranibizumab (intravitreal injections) in patients with visual impairment due to diabetic macular edema; RIDE: Ranibizumab injection in subjects with clinically significant macular edema (ME) with center involvement secondary to diabetes mellitus; RISE: ranibizumab injection in subjects with clinically significant macular edema (ME) with center involvement secondary to diabetes mellitus

1. Ding J, Wong TY, Current epidemiology of diabetic retinopathy and diabetic macular edema, *Curr Diab Rep*, 2012;12:346–54.
2. International Diabetes Federation, IDF Diabetes Atlas, 7th edition. Available at: www.diabetesatlas.org/ (accessed 4 July 2016).
3. Chen E, Looman M, Laouri M, et al., Burden of illness of diabetic macular edema: literature review, *Curr Med Res Opin*, 2010;26:1587–97.
4. Sabanayagam C, Yip W, Ting DS, et al., Ten Emerging Trends in the Epidemiology of Diabetic Retinopathy, *Ophthalmic Epidemiol*, 2016;1–14.
5. Dedania VS, Bakri SJ, Current perspectives on ranibizumab, *Clin Ophthalmol*, 2015;9:533–42.
6. Fong AH, Lai TY, Long-term effectiveness of ranibizumab for age-related macular degeneration and diabetic macular edema, *Clin Interv Aging*, 2013;8:467–83.
7. Frampton JE, Ranibizumab: in diabetic macular oedema, *Drugs*, 2012;72:509–23.
8. Krispel C, Rodrigues M, Xin X, et al., Ranibizumab in diabetic macular edema, *World J Diabetes*, 2013;4:310–8.
9. Wang H, Sun X, Liu K, et al., Intravitreal ranibizumab (lucentis) for the treatment of diabetic macular edema: a systematic review and meta-analysis of randomized clinical control trials, *Curr Eye Res*, 2012;37:661–70.
10. Yanagida Y, Ueta T, Systemic safety of ranibizumab for diabetic macular edema: meta-analysis of randomized trials, *Retina*, 2014;34:629–35.
11. Berger A, Sheidow T, Cruess AF, et al., Efficacy/safety of ranibizumab monotherapy or with laser versus laser monotherapy in DME, Canadian journal of ophthalmology, *Can J Ophthalmol*, 2015;50:209–16.
12. Bressler SB, Glassman AR, Almukhtar T, et al., Five-Year Outcomes of Ranibizumab With Prompt or Deferred Laser Versus Laser or Triamcinolone Plus Deferred Ranibizumab for Diabetic Macular Edema, *Am J Ophthalmol*, 2016;164:57–68.
13. Chong V, Mitchell P, Baseline predictors of 3-year responses to ranibizumab and laser photocoagulation therapy in patients with visual impairment due to diabetic macular edema (DME), *Eur J Ophthalmol*, 2013;23:453–4.
14. Elman MJ, Aiello LP, Beck RW, et al., Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema, *Ophthalmology*, 2010;117:1064–77.e35.
15. Elman MJ, Ayala A, Bressler NM, et al., Intravitreal Ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results, *Ophthalmology*, 2015;122:375–81.
16. Ishibashi T, Li X, Koh A, et al., The REVEAL Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema, *Ophthalmology*, 2015;122:1402–15.
17. López-Gálvez MI, Arias L, Roura M, Efficacy and safety profile of ranibizumab versus laser photocoagulation in patients with diabetic macular edema. Re-Des Study, *Ophthalmologica*, 2014;232:15.
18. Mitchell P, Bandello F, Schmidt-Erfurth U, et al., The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema, *Ophthalmology*, 2011;118:615–25.
19. Régnier S, Malcolm W, Allen F, et al., Efficacy of anti-VEGF and laser photocoagulation in the treatment of visual impairment due to diabetic macular edema: a systematic review and network meta-analysis, *PloS one*, 2014;9:e102309.
20. Hutton D, Newman-Casey PA, Tavag M, et al., Switching to less expensive blindness drug could save medicare part B $18 billion over a ten-year period, *Health Aff* (Millwood), 2014;33:931–9.
21. Pershing S, Enns EA, Matesic B, et al., Cost-effectiveness of treatment of diabetic macular edema, *Ann Intern Med*, 2014;160:18–29.
22. Shaughnessy AF, Monoclonal antibodies: magic bullets with a hefty price tag, *BMJ*, 2012;345:e8346.
23. Campochiaro PA, Khanani A, Singer M, et al., Enhanced Benefit in Diabetic Macular Edema from AKB-9778 Tie2 Activation Combined with Vascular Endothelial Growth Factor Suppression, *Ophthalmology*, 2016;.
24. Ciulla TA, Hussain RM, Ciulla LM, et al., Ranibizumab for diabetic macular edema refractory to multiple prior treatments, *Retina*, 2016;36:1292-7.
25. Wells JA, Glassman AR, Ayala AR, et al., Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial, *Ophthalmology*, 2016;123:1351–9.
26. Wiley HE, Thompson DJ, Bailey C, et al., A Crossover Design for Comparative Efficacy: A 36-Week Randomized Trial of Bevacizumab and Ranibizumab for Diabetic Macular Edema, *Ophthalmology*, 2016;123:841–9.
27. Boyer DS, Nguyen QD, Brown DM, et al., Outcomes with As-Needed Ranibizumab after Initial Monthly Therapy: Long-Term Outcomes of the Phase III RIDE and RISE Trials, *Ophthalmology*, 2015;122:2504–13.e1.
28. Brown DM, Nguyen QD, Marcus DM, 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.
29. Do DV, Sepah YJ, Boyer D, et al., Month-6 primary outcomes of the READ-3 study (Ranibizumab for Edema of the mAcula in Diabetes-Protocol 3 with high dose), *Eye (Lond)*, 2015;29:1538–44.
30. Ghanchi F, Hazel CA, South Asian diabetic macular oedema treated with ranibizumab (ADMOR)-real-life experience, *Eye (Lond)*,2016;30:133–8.
31. Massin P, Bandello F, Garweg JG, 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.
32. Menchini U, Bandello F, De Angelis V, et al., Ranibizumab for Visual Impairment due to Diabetic Macular Edema: Real-World Evidence in the Italian Population (PRIDE Study), *J Ophthal*, 2015;2015:324841.
33. Nguyen QD, Shah SM, Heier JS, et al., Primary End Point (Six Months) Results of the Ranibizumab for Edema of the mAcula in diabetes (READ-2) study, *Ophthalmology*, 2009;116:2175–81.e1.
34. Pearce I, Banerjee S, Burton BJL, et al., Ranibizumab 0.5 mg for Diabetic Macular Edema with Bimonthly Monitoring after a Phase of Initial Treatment: 18-Month, Multicenter, Phase IIIB RELIGHT Study, *Ophthalmology*, 2015;122:1811–9.
35. Prünte C, Fajnkuchen F, Mahmood S, et al., Ranibizumab 0.5 mg treat-and-extend regimen for diabetic macular oedema: the RETAIN study, *Br J Ophthalmol*, 2016;100:787–95.
36. Dhoot DS, Pieramici DJ, Nasir M, et al., Residual edema evaluation with ranibizumab 0.5 mg and 2.0 mg formulations for diabetic macular edema (REEF study), *Eye (Lond)*, 2015;29:534–41.
37. Bressler NM, Varma R, Suner IJ, et al., Vision-Related Function after Ranibizumab Treatment for Diabetic Macular Edema, *Ophthalmology*, 2014;121:2461–72.
38. Brown GC, Brown MM, Turpcu A, et al., The Cost-Effectiveness of Ranibizumab for the Treatment of Diabetic Macular Edema, *Ophthalmology*, 2015;122:1416–25.
39. Régnier SA, Malcolm W, Haig J, et al., Cost-effectiveness of ranibizumab versus aflibercept in the treatment of visual impairment due to diabetic macular edema: a UK healthcare perspective, *CEOR*, 2015;7:235–47.
40. Zhang X, Saaddine JB, Chou CF, et al., Prevalence of diabetic retinopathy in the United States, 2005-2008, *JAMA*, 2010;304:649–56.
41. Hernandez C, Candell-Riera J, Ciudin A, et al., Prevalence and risk factors accounting for true silent myocardial ischemia: a pilot case-control study comparing type 2 diabetic with non-diabetic control subjects, *Cardiovasc Diabetol*, 2011;10:9.