The relative clinical effectiveness of ranibizumab and bevacizumab in diabetic macular oedema: an indirect comparison in a systematic review
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CRD summary
This review concluded that there appeared to be no difference in effectiveness between ranibizumab and bevacizumab for the treatment of diabetic macular oedema, but the wide credible intervals could not exclude the possibility that either drug might be superior. This was a well-conducted review and the authors' conclusions are appropriate.

Authors' objectives
To indirectly compare the effectiveness of ranibizumab and bevacizumab in the treatment of diabetic macular oedema.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1996 to September 2011; search terms were reported. There were no language restrictions. ClinicalTrials.gov and the European Union Clinical Trials Register were searched in an attempt to identify unpublished studies. The abstracts of some relevant meetings were also searched from 2002 to November 2011.

Study selection
Randomised controlled trials (RCTs) that assessed ranibizumab or bevacizumab for the treatment of diabetic macular oedema and that measured best corrected visual acuity were eligible for inclusion. RCTs were excluded if patients in one or more treatment arms underwent surgical procedures, such as cataract removal.

Eligible studies were assessed for common comparators. Amongst studies with a common comparator, the similarity of the studies was assessed based on four criteria: baseline patient population; administration and frequency of common comparator; outcomes assessment; and length of follow-up. One network was found to be similar enough for indirect comparison; studies that compared ranibizumab or bevacizumab with multiple laser photocoagulation.

The included studies compared 1.25 mg intravitreal bevacizumab (with or without sham laser) with laser therapy (with or without sham injection) or 0.5 mg intravitreal ranibizumab (with or without sham laser) with laser therapy (with or without sham injection). Frequency of treatment ranged from monthly to four monthly, or as required. Best corrected visual acuity was the primary outcome in all of the included trials. Patients had eyes with clinically significant macular oedema (with or without previous laser treatment) or diabetic macular oedema. Studies were conducted in the UK, Iran, the USA or were international multicentre trials.

Two reviewers assessed article titles for eligibility; it was unclear whether two reviewers also assessed full papers.

Assessment of study quality
Risk of bias was assessed using the Cochrane risk of bias tool.

The authors did not state how many reviewers undertook the assessment.

Data extraction
Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the proportion of patients with an improvement in best corrected visual acuity of more than two lines (or 10 letters) on the Early Treatment Diabetic Retinopathy Study scale. Mean differences (MD) with 95% confidence intervals were calculated for mean change from baseline in best corrected visual acuity (logarithm of the minimum angle of resolution logMAR) and mean change from baseline in central macular thickness. Data were also collected on adverse events. Best corrected visual acuity data was converted to logMAR units, a linear scale of visual acuity with positive values representing increased visual loss.

Data were extracted by one reviewer and checked by a second. Study authors were contacted for missing data, when required.
Methods of synthesis
For direct evidence (ranibizumab versus laser therapy and bevacizumab versus laser therapy) odds ratios and mean differences were pooled using meta-analysis. The level of heterogeneity was assessed using $I^2$. The results were used to assess for heterogeneity and were also compared with the results of the indirect comparison to assess for consistency.

An indirect comparison of ranibizumab versus bevacizumab was performed for each outcome using Bayesian Markov chain Monte Carlo methods and a random-effects simulation model, a level of between-study heterogeneity observable in the available data was assumed. Ninety-five percent credible intervals were also reported.

Assumptions related to heterogeneity and consistency were assessed using the methods of Song et al. Differences in length of follow-up between studies were addressed in the analysis of the proportion of patients with improved vision by fitting a binomial likelihood model with a complementary log-log link function. Normal likelihood models with identity link functions were used in the comparisons of best corrected visual acuity and central macular thickness to calculate mean differences between interventions.

Secondary analyses were conducted to compare bevacizumab alone with ranibizumab plus prompt laser or ranibizumab plus deferred laser.

Results of the review
Five RCTs (1,555 eyes) with a common comparator were sufficiently similar to be included in the indirect comparison. The RCTs were generally good quality; four studies reported appropriate methods of randomisation and all studies were free from selective reporting. However, only three RCTs were appropriately blinded, and only one RCT described adequate allocation concealment. Length of follow-up was six months in two studies and 12 months in three studies.

In the direct evidence meta-analysis the proportion with improvement in best corrected visual acuity and the mean change in best-corrected visual acuity were statistically significantly higher for bevacizumab than laser therapy (OR 4.2, 95% CI 1.6 to 11.4 and MD -0.21, 95% CI -0.29 to -0.13, respectively; two RCTs) with no significant heterogeneity ($I^2=0\%$). The proportion with improvement in best corrected visual acuity and the mean change in best-corrected visual acuity were statistically significantly higher for ranibizumab than laser therapy (OR 6.0, 95% CI 1.4 to 26.4 and MD -0.13, 95% CI -0.18 to -0.08, respectively; two RCTs), but there was significant heterogeneity for the first outcome ($I^2=69\%$). There was no significant difference between treatment groups for mean change in central macular thickness.

In the indirect comparison main analysis there was no statistically significant difference between bevacizumab and ranibizumab in the proportion with improvement in best corrected visual acuity, the mean change in best-corrected visual acuity, the mean change in central macular thickness. Results for secondary analyses were also not statistically significant. There was no evidence of inconsistency in the network and the residual deviance statistics indicated a good model fit.

There was no consistent increase in adverse events (in terms of cardiovascular events, hypertension, endophthalmitis or intraocular pressure hypertension) in either of the treatment groups. The highest proportion of adverse events was seen with sham injection and/or laser.

Authors' conclusions
There appeared to be no difference in effectiveness between ranibizumab and bevacizumab for the treatment of diabetic macular oedema, but the wide credible intervals could not exclude the possibility that either drug might have been superior.

CRD commentary
The review question and inclusion criteria were clear. The search strategy was thorough and reduced the potential for language and publication bias. Screening article titles for eligibility and data extraction procedures were undertaken by two reviewers, which reduced the potential for error and bias, but it was unclear whether the screening of full papers and the quality assessment were undertaken by two reviewers.

Study quality was assessed appropriately and full results were reported. The methods used for pooling studies appear to have been appropriate, but the authors acknowledged that indirect comparisons are subject to potential biases and should be interpreted with caution. The authors also acknowledged that the included studies were of low statistical
power which, coupled with moderate heterogeneity between studies, resulted in wide credible intervals around estimates of treatment effects.

This was a well-conducted review and the authors' conclusions are appropriate.

**Implications of the review for practice and research**

**Practice:** The authors stated that clinicians and policy makers could face the dilemma of choosing between an unlicensed treatment for diabetic macular oedema (bevacizumab) versus an expensive licensed alternative (ranibizumab) with similar outcomes.

**Research:** The authors stated that a long-term, sufficiently powered, direct head-to-head trial that compared bevacizumab with ranibizumab for the treatment of diabetic macular oedema was needed. This should also examine the place of laser therapy in the treatment pathway. They also stated that large scale safety studies of bevacizumab with ranibizumab were needed.

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contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.