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Fenofibrate for diabetic retinopathy

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Fenofibrate for diabetic retinopathy

Kana Inoue^{1a}, Sachiko Y Kataoka², Sumihiro Kawano³, Toshi A Furukawa⁴, Noemi Lois^{5b}, Norio Watanabe⁴

¹Epidemiology and Preventive Service, Kyoto University, Kyoto, Japan. ²Department Healthcare Epidemiology, Kyoto University School of Public Health, Kyoto, Japan. ³Ophthalmology, Kagoshima University, Kagoshima, Japan. ⁴Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan. ⁵Wellcome-Wolfson Institute for Experimental Medicine, Queen's University, Belfast, UK

^aThese authors contributed equally to this work. ^bThese authors contributed equally to this work

Contact address: Kana Inoue, Epidemiology and Preventive Service, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto, 606-8501, Japan. k.inoue333@gmail.com.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To investigate the effects of fenofibrate on the prevention and progression of diabetic retinopathy.

BACKGROUND

Description of the condition

Globally, from an overall 32.4 million blind and 191 million visually impaired people, 0.8 million were blind and 3.7 million were visually impaired due to diabetic retinopathy in 2010 (Leasher 2016). Age-standardised prevalence of diabetic retinopathy-related blindness or visual impairment was higher in sub-Saharan Africa and South Asia (Leasher 2016). Extrapolated to the world diabetes population in 2010, one study has estimated that approximately 93 million people may have any diabetic retinopathy, and 28 million people may have sight-threatening stages of diabetic retinopathy (Yau 2012). In addition to constituting a physical burden to patients, society bears an economic burden because of treating diabetic retinopathy. Several studies in Europe, USA and Asia have recently reported association of higher medical costs with di-

abetic retinopathy (Heintz 2010; Romero-Aroca 2016; Schmier 2009; Woung 2010; Zhang 2017). The total healthcare costs of diabetic retinopathy in Sweden is up to approximately EUR 9.9 million per year, and the annual cost for diabetic retinopathy was EUR 106,000 per 100,000 inhabitants when considering a 4.8% prevalence of diabetes (Heintz 2010). A study in Singapore reported that the presence and severity of diabetic retinopathy was associated with increased direct medical costs (Zhang 2017).

Description of the intervention

Diabetic retinopathy is the most common microvascular complication of diabetes, in which high blood sugar leads to damage of the blood vessels in the retina. The cells (endothelial cells and pericytes) in the small retinal blood vessels (capillaries) are lost as a result of diabetes and these 'acellular' capillaries are non-functioning with a subsequent reduction or cessation of blood supply

to the retina. As the blood vessels become weak, fluid contained in them also leaks out, leading to oedema (accumulation of fluid) in the retina. When the fluid accumulates in the centre of the retina, the macula, diabetic macular oedema (DMO) ensues (Tan 2017). The lack of blood supply to the retina is compensated by the retina forming 'new vessels', which are abnormal and fragile; this is known as proliferative diabetic retinopathy (PDR) (Evans 2014).

Strict control of blood glucose levels and blood pressure is essential to reduce the risk of sight loss as a result of the complications of diabetic retinopathy, namely DMO and PDR but is often difficult to achieve. In some people with diabetes, DMO and PDR may still occur even if glucose levels and blood pressure are well controlled. Laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents and corticosteroids are used to treat DMO and PDR (Duh 2017; Evans 2014; Gross 2015; McCulloch 2017). Therapeutic strategies to prevent the development of the end-stage complications of diabetic retinopathy are, though, lacking and very much needed.

Fenofibrate, a fibrate indicated for mixed dyslipidaemia and hypertriglyceridaemia, came on to the market in 1975, and is widely used in over 90 low-, middle- and high-income countries. Its cost is quite low, for example, the equivalent of INR 90 a day in India. The main clinical effects are mediated by peroxisome proliferator-activated receptor (PPAR) α activation and consist of a moderate reduction in total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels, a marked reduction in triglycerides (TG) and an increase in high-density lipoprotein cholesterol (HDL-C).

How the intervention might work

Fenofibrate is a peroxisome proliferator-activated receptor α agonist (PPAR- α). PPAR- α is highly expressed in tissues with high mitochondrial and peroxisomal fatty-acid β -oxidation rates, such as the retina (Ciudin 2013). It has been reported that PPAR- α is downregulated in the retinas of both type 1 and type 2 diabetic models and that high glucose is a cause of PPAR- α downregulation (Hu 2013). PPAR- α knockout mice develop vascular leakage, leukostasis, pericyte loss, capillary degeneration and overexpression of inflammatory markers (Hu 2013), all features observed in diabetic retinopathy in humans. Therefore, fenofibrate may help reverse the effects of diabetes in the retina. Other reported mechanisms through which fenofibrate may ameliorate diabetic retinopathy include modulating Nrf2 signalling and NLRP3 inflammasome activation, and by cytochrome P450 Epoxygenase (CYP)2C inhibition (Gong 2016; Liu 2017).

Why it is important to do this review

The number of people with diabetes as well as the number of people suffering from diabetic retinopathy is increasing worldwide. As described above, laser photocoagulation, anti-VEGFs and steroids are only used for the treatment of established DMO and PDR (Aiello 2010; Boyer 2014; Gross 2015; Sivaprasad 2017; Virgili 2017), but not to prevent their occurrence nor to prevent the development and progression of diabetic retinopathy. Fenofibrate may be useful for this purpose.

OBJECTIVES

To investigate the effects of fenofibrate on the prevention and progression of diabetic retinopathy.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) only.

Types of participants

Participants will be people diagnosed with type 1 or 2 diabetes. We will include those who do not have retinopathy or who had diabetic retinopathy at baseline.

Types of interventions

Intervention: fenofibrate (any dose/regimen)

Comparison: placebo or observation

Types of outcome measures

Studies will not be excluded if no outcome data are available, unless it is clear that none of the following outcomes were measured.

Primary outcomes

- Progression of diabetic retinopathy

'Progression' is defined as moving from no previously overt retinopathy to any overt retinopathy; or, for people with any overt retinopathy already present, advancing two or more steps in the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale, based on evaluation of stereoscopic or non-stereoscopic colour fundus photographs of participants who had diabetic retinopathy at baseline (ETDRS Research Group 1991).

Secondary outcomes

- Incidence of overt retinopathy
- Mean change in visual acuity
- Proportion of participants with a reduction in visual acuity of 10 ETDRS letters or more
- Incidence of PDR
- Incidence of DMO
- Additional treatments for diabetic retinopathy (focal/grid laser, panretinal photocoagulation, anti-VEGFs, steroids, vitrectomy, other)
- Mean vision-related quality of life
- Incremental cost per Quality Adjusted Life years (QALY) gained
- Acceptability of the treatment
- Proportion of participants in which treatment is discontinued

All outcomes will be considered at one, three and five years (plus or minus six months for each time point).

Adverse effects

Rhabdomyolysis, hepatic disorder, pancreatitis, Stevens-Johnson Syndrome and any others that are reported. We will use the original study authors' definitions for serious adverse events.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for randomised controlled trials and controlled clinical trials. There will be no restrictions on language or year of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (latest issue) ([Appendix 1](#)).
- MEDLINE Ovid (1946 to present) ([Appendix 2](#)).
- Embase Ovid (1980 to present) ([Appendix 3](#)).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch) ([Appendix 4](#)).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) ([Appendix 5](#)).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) ([Appendix 6](#)).

Searching other resources

We (KI, SYK, SK) will search the reference lists of identified clinical trials. We will perform an additional handsearch for proceedings of scientific meetings focusing on retinopathy, ophthalmology and diabetes.

We will handsearch the European Association for the Study of Diabetes (EASD) congress and the European Association for the Study of Diabetes Eye Complications Study Group (EASDEC) congress from 1990 to the present.

Data collection and analysis

We will conduct trial selection, data extraction and management using [Covidence](#).

Selection of studies

Three review authors (KI, SYK, SK) will independently screen the search results and select trials for inclusion. We will resolve disagreements through discussion. We will screen the list of citations and abstracts and classify records into 'possibly relevant' and 'definitely not relevant'. For the records we identify as 'possibly relevant' we will obtain the full-text articles. Following the [Criteria for considering studies for this review](#) section, we will classify trials into 'to be included' or 'to be excluded'. We will give the primary reasons for exclusion in the Excluded studies table.

Data extraction and management

Two review authors (KI, SK) will independently extract data from trial reports and enter the data into Review Manager 5 (RevMan 5) ([Review Manager 2014](#)). Where information available from the full-text articles is insufficient, we will contact the original trial authors to request additional information. We will resolve any differences in opinion through discussion. If we cannot reach consensus, we will consult a third review author (SYK). We will use a data collection form ([Appendix 7](#)), and plan to pilot the form. We will obtain English translations of any trial reported in a language other than English before extracting data. We will obtain the following data on outcomes specified in [Types of outcome measures](#): for dichotomous outcomes, we will collect data on the number of events and total participants randomised as well as followed up in each trial arm; for continuous outcomes, we will collect data on the mean and standard deviation in each trial arm.

Assessment of risk of bias in included studies

Three review authors (KI, SYK, SK) will independently assess study quality, study limitations and the extent of potential bias by using the Cochrane 'Risk of bias' tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2017](#)). We will consider the following domains.

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Masking (blinding) of participants, personnel and outcomes assessors (performance and detection bias)
- Incomplete outcome data (attrition bias)
- Selective outcome reporting (reporting bias)
- Other - other threats to validity

For each domain, we will judge whether the trial authors have made sufficient attempts to minimise bias in their study design. We will make judgements using three measures: high, low and unclear risk of bias. We will record this judgement in the 'Risk of bias' tables and will present a summary 'Risk of bias' figure.

Measures of treatment effect

We will measure treatment effect according to the data types described in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Dichotomous data

Variables in this group include the primary outcome, progression of diabetic retinopathy. Variables in this group also include the secondary outcomes, incidence of overt retinopathy, proportion of participants with a reduction in visual acuity of 10 ETDRS letters or more, incidence of PDR, incidence of DMO, acceptability of the treatment and proportion of participants in which treatment is discontinued. We will report dichotomous variables as risk ratios (RRs) with 95% confidence intervals (CIs).

Continuous data

We will report continuous variables including difference between groups on mean change of visual acuity, quality-of-life scores, incremental cost per QALY gained as mean difference with 95% CI (if normally distributed) or median and interquartile range (if not normally distributed). We will calculate the standardised mean difference (SMD) when trials use different scales for the same outcome assessment.

Unit of analysis issues

We anticipate that studies will be individually randomised trials where people are allocated to fenofibrate or control.

Trials reporting one eye per person

There is no unit of analysis issue. We will document how the trials selected the eye to be included in the study. .

Trials reporting two eyes per person

Ideally such studies will adjust for within-person correlation. If so, we will collect data on the measure of effect and confidence interval and enter this into RevMan 5 using the generic inverse variance method (Review Manager 2014). If trials reported both eyes without this adjustment, we will use these data and discuss the implications of this in the interpretation.

Dealing with missing data

When there are missing data, we will contact the authors of the primary trials to obtain the missing data and the reason why the data are missing. If it is not possible to obtain the missing data, we will explain why we could not get them. We will document when loss to follow-up was high (over 20%), or unbalanced between treatment groups, as a potential source of attrition bias. We will use data as reported in the trial reports, including any imputation for missing data.

Assessment of heterogeneity

We will assess heterogeneity between trials by visual inspection of forest plots, and by formal statistical tests of heterogeneity (Chi² test (Deeks 2017)). If there is evidence of substantial heterogeneity (defined as I² statistic greater than 50% (Higgins 2003)), and sufficient numbers of trials are available (i.e. 10), we will explore the possible reasons for heterogeneity using subgroup and sensitivity analyses.

Assessment of reporting biases

We will search both registered trials and published trials, and we will report the proportion of unpublished trials among registered trials. We will contact researchers of the unpublished trials to provide data related to outcomes in this review. If we cannot obtain the data, we will describe them in the review. If we include 10 studies or more in the meta-analysis, we will create a funnel plot and interpret asymmetry as indicating possible publication bias (Sterne 2017).

Data synthesis

We plan to perform statistical analyses according to guidance from Cochrane Eyes and Vision. We will pool data using a random-effects model, unless there are three or fewer trials, in which case we will use a fixed-effect model. In case of substantial clinical or statistical heterogeneity, we will not combine study results but present a narrative or tabulated summary.

Subgroup analysis and investigation of heterogeneity

If a sufficient number of studies is available, we will perform the following subgroup analyses to investigate whether the presence or absence of particular covariates explains the variability in effect sizes.

- Type of diabetes (type 1 or type 2)
- Age groups (65 years or younger, or older than 65 years)
- With or without dyslipidaemia at baseline (TG 150 mg/dL or more than 150mg/dl, or less than 150 mg/dL)
- With or without overt retinopathy at baseline (the ETDRS Final Retinopathy Severity Scale for Persons of step 3 or less, or step 4 or greater)
- Local treatments used (laser photocoagulation and/or anti-VEGFs and/or intravitreal steroids)
- The severity of diabetes (HbA1c 7.0% or more than 7.0%, or less than 7.0%)

Sensitivity analysis

We plan to perform sensitivity analyses for the following factors if applicable.

- We will include only studies of adequate methodology (low risk of bias), defined as adequate randomisation and allocation concealment, using proper methods for dealing with incomplete outcome data and masking of intervention and measurement.
- We will exclude industry-funded studies and see whether it makes a difference to the effect estimate.

Summary of findings

We will report absolute risks and measures of effect in a 'Summary of findings' table, providing an overall assessment of the certainty of the evidence for each outcome using the GRADE system (GRADEpro GDT 2015). Three review authors (KI, SYK, SK) will independently perform the GRADE assessment.

We plan to include the following outcomes in the 'Summary of findings' tables. We will report these outcomes at three years.

- Progression of retinopathy
- Incidence of overt retinopathy
- Proportion of participants with visual acuity loss of 10 ETDRS letters or more
- Incidence of PDR
- Incidence of DMO
- Vision-related quality of life
- Adverse effects

ACKNOWLEDGEMENTS

Cochrane Eyes and Vision (CEV) will create and execute the electronic search strategies. We thank Emily Chew and Jennifer Evans for their comments on this protocol and Anupa Shah for her assistance throughout the editorial process.

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Tan 2017

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Zhang 2017

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* Indicates the major publication for the study

APPENDICES**Appendix 1. CENTRAL search strategy**

- #1 MeSH descriptor: [Diabetic Retinopathy] explode all trees
- #2 (diabet* or proliferative or non-proliferative) near/4 retinopath*
- #3 diabet* near/3 (eye* or vision or visual* or sight*)
- #4 retinopath* near/3 (eye* or vision or visual* or sight*)
- #5 DR near/3 (eye* or vision or visual* or sight*)
- #6 #1 or #2 or #3 or #4 or #5
- #7 MeSH descriptor: [Fenofibrate] this term only
- #8 fenofibrate or phenofibrate
- #9 antara or controlip or durafenat or fenoglide or fenobeta or fenofanton or lipofen or lipanthyl or lipantil or liparison or livesan or lofibra or normalip or procetofen or procetofene or secalap or supralip or tricor or triglide
- #10 #7 or #8 or #9
- #11 #6 and #10

Appendix 2. MEDLINE Ovid search strategy

- 1. randomized controlled trial.pt.
- 2. random\$.ab,ti.
- 3. placebo.ab,ti.
- 4. dt.fs.
- 5. trial.ab,ti.
- 6. (group or groups).ab,ti.
- 7. or/1-6
- 8. exp animals/
- 9. exp humans/
- 10. 8 not (8 and 9)
- 11. 7 not 10
- 12. exp Diabetic Retinopathy/
- 13. ((diabet\$ or proliferative or non-proliferative) adj4 retinopath\$).tw.
- 14. diabetic retinopathy.kw.
- 15. (diabet\$ adj3 (eye\$ or vision or visual\$ or sight\$)).tw.
- 16. (retinopath\$ adj3 (eye\$ or vision or visual\$ or sight\$)).tw.
- 17. (DR adj3 (eye\$ or vision or visual\$ or sight\$)).tw.
- 18. or/12-17

19. Fenofibrate/
20. (fenofibrate or phenofibrate).tw.
21. (antara or controlip or durafenat or fenoglide or fenobeta or fenofanton or lipofen or lipanthyl or lipantil or liparison or livesan or lofibra or normalip or procetofen or procetofene or secalap or supralip or tricolor or triglide).tw.
22. or/19-21
23. 18 and 22
24. 11 and 23

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by [Glanville 2006](#).

Appendix 3. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$).tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control\$ or prospectiv\$ or volunteer\$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp Diabetic Retinopathy/
34. ((diabet\$ or proliferative or non-proliferative) adj4 retinopath\$).tw.
35. diabetic retinopathy.kw.
36. (diabet\$ adj3 (eye\$ or vision or visual\$ or sight\$)).tw.
37. (retinopath\$ adj3 (eye\$ or vision or visual\$ or sight\$)).tw.
38. (DR adj3 (eye\$ or vision or visual\$ or sight\$)).tw.
39. or/33-38
40. Fenofibrate/
41. (fenofibrate or phenofibrate).tw.

42. (antara or controlip or durafenat or fenoglide or fenobeta or fenofanton or lipofen or lipanthyl or lipantil or liparison or livesan or lofibra or normalip or procetofen or procetofene or secalap or supralip or tricor or triglide).tw.

43. or/40-42

44. 39 and 43

45. 32 and 44

Appendix 4. ISRCTN search strategy

(fenofibrate OR phenofibrate OR tricor) AND diabetic retinopathy

Appendix 5. ClinicalTrials.gov search strategy

(fenofibrate OR phenofibrate OR tricor) AND (diabetic retinopathy)

Appendix 6. WHO ICTRP search strategy

diabetic retinopathy = Condition AND fenofibrate OR phenofibrate OR tricor = Intervention

Appendix 7. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	<ul style="list-style-type: none"> • Parallel-group RCT<i>i.e. people randomised to treatment</i> • Cluster-RCT<i>i.e. communities randomised to treatment</i> • Cross-over RCT • Other, specify Exclusions after randomisation Losses to follow-up Number randomised/analysed How were missing data handled? <i>e.g., available case analysis, imputation methods</i> Reported power calculation (Y/N), <i>if yes, sample size and power</i> Unusual study design/issues	
Eyes <i>or</i> Unit of randomisation/ unit of analysis	Two eyes included in study, both eyes received same treatment, briefly specify how analysed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye	

(Continued)

Participants		
Country		Setting
Total number of participants	<i>This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up only, please indicate.</i>	Ethnic group
Number (%) of men and women		Equivalence of baseline characteristics (Y/
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n=) Comparator (n=)	<ul style="list-style-type: none"> • Number of people randomised to this group • Drug (or intervention) name • Dose • Frequency • Route of administration 	
Outcomes		
Primary and secondary outcomes <i>as defined in study reports</i>	List outcomes Adverse events reported (Y/N) Length of follow-up and intervals at which outcomes assessed	Planned/actual length of follow-up
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: <i>(if applicable)</i> Reported subgroup analyses (Y/N) Were trial investigators contacted?
Sources of funding		
Declaration of interest		

CONTRIBUTIONS OF AUTHORS

KI produced the first draft of the protocol. NL edited subsequent drafts.

SYK, SK, TAF and NW reviewed and commented on subsequent drafts.

DECLARATIONS OF INTEREST

KI: none known

SYK: none known

SK: none known

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NL: none known

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