# Low prevalence of fibrate use in adults with type 1 and type 2 diabetes and established diabetic retinopathy

Diabetic retinopathy (DR) is common, with estimated prevalences of 25% (type 2 diabetes [T2D]) and 77% (type 1 diabetes [T1D]).[1] The estimated 10-year cumulative incidence of DR is 67% (T2D not on insulin), 79% (T2D on insulin), and 89% (T1D)[2] and at 25 years is 97% (T1D).[3] DR comprises 3 processes: (*i*) nonproliferative DR (microaneurysms, intraretinal hemorrhages, intraretinal microvascular anomalies) and proliferative DR (neovascularization, vitreous hemorrhage, tractional retinal detachment); (*ii*) diabetic macular edema (ME), from vessel leakage within the macula; and (*iii*) macular ischemia.[4] Because DR may be asymptomatic, routine screening is recommended.[4,5] Early DR identification is important as effective treatments exist to prevent or delay DR-related vision loss: optimal glycemic and blood pressure control, laser photocoagulation, anti-vascular endothelial growth factor therapy, and fenofibrate.[4] Evidence from the FIELD[6] and ACCORD-Eye[7] studies support fenofibrate use to improve eye outcomes. Thus, Diabetes Canada recommends that "fenofibrate, in addition to statin therapy, may be used in people with T2D to slow the progression of established retinopathy" (grade A level 1A recommendation).[4] Although the Canadian Ophthalmological Society does not formally recommend fenofibrate, it notes Diabetes Canada's recommendation for lipid control.[5]

There is a dearth of studies assessing fibrate utilization in DR. We hypothesized that people with DR are underprescribed fenofibrate. The primary study objective was to determine prevalence of fibrate use in DR at our tertiary care centre. The secondary objective was to determine fibrate use predictors. This was a single-centre cross-sectional study at St. Joseph's Healthcare London in London, Canada. Data were extracted in November 2018 from WebDR, a diabetes-specific electronic medical record database in routine clinical use since 2011, housing ~25,000 unique patient records. Adults aged ≥18 years with T1D or T2D with DR were eligible for inclusion. DR was defined as the presence in WebDR of ≥1 of: retinopathy, ME, clinically significant ME, laser photocoagulation, vitrectomy, or blindness/vision loss, ascertained via patient self-report during routine clinical care and/or optometrist/ophthalmologist report. Fibrate use was defined as inclusion of fenofibrate, bezafibrate, or gemfibrozil in the current medications. Descriptive statistics were compared using Welch's *t* test or Fisher's exact test as appropriate. Hierarchical logistic regression was performed to determine fibrate use predictors. Estimated odds ratios and 95% confidence intervals were calculated using Firth's correction and the profile likelihood

**Table 1—Univariate analyses—patient characteristics**

| | Total (n = 1341) | No Fibrate (n = 1301) | Fibrate (n = 40) | *p* Value |
|---|---|---|---|---|
| Male sex | 736 (54.9) | 714 (54.9) | 22 (55.0) | 0.988 |
| Age (y), mean (SD) | 63.0 (15.5) | 62.8 (15.6) | 69.2 (13.1) | 0.004‡ |
| Type 1 diabetes | 506 (37.7) | 502 (38.6) | 4 (10.0) | <0.001‡ |
| Duration of diabetes (y), mean, (SD) | 29.7 (12.8) | 29.7 (12.8) | 28.4 (10.9) | 0.450 |
| Followed by family physician diabetologist | 296 (22.1) | 282 (21.7) | 14 (35.0) | 0.053 |
| HbA1c (%), mean (SD) | 8.2 (2.6) | 8.2 (2.6) | 8.0 (1.7) | 0.500 |
| LDL-cholesterol (mmol/L), mean (SD) | 1.90 (0.82) | 1.90 (0.82) | 1.83 (0.94) | 0.640 |
| Triglyceride (mmol/L), mean (SD) | 1.61 (1.11) | 1.59 (1.10) | 2.30 (1.02) | <0.001‡ |
| HDL-cholesterol (mmol/L), mean (SD) | 1.32 (0.46) | 1.33 (0.46) | 1.01 (0.32) | <0.001‡ |
| Nonproliferative DR | 375 (28.0) | 358 (27.5) | 17 (42.5) | 0.120 |
| Severe DR* | 589 (43.9) | 574 (44.1) | 15 (37.5) | |
| DR/macular edema not otherwise specified | 377 (28.1) | 369 (28.4) | 8 (20.0) | |
| Hypertension | 924 (68.9) | 886 (68.1) | 38 (95.0) | <0.001‡ |
| Dyslipidemia (other than hypertriglyceridemia) | 983 (73.3) | 946 (72.7) | 37 (92.5) | 0.003‡ |
| Coronary artery disease | 333 (24.8) | 319 (24.5) | 14 (35.0) | 0.14 |
| Cerebrovascular disease | 145 (10.8) | 138 (10.6) | 7 (17.5) | 0.19 |
| Chronic kidney disease | 504 (37.6) | 486 (37.4) | 18 (45.0) | 0.053 |
| End-stage renal disease or renal transplant | 128 (9.5) | 126 (9.7) | 2 (5.0) | |
| Peripheral vascular disease | 102 (7.6) | 95 (7.3) | 7 (17.5) | 0.028‡ |
| Statin use | 1023 (76.3) | 993 (76.3) | 30 (75.0) | 0.850 |
| ACE-I or ARB use | 946 (70.5) | 911 (70.0) | 35 (87.5) | 0.020‡ |
| ASA use | 599 (44.7) | 582 (44.7) | 17 (42.5) | 0.087 |
| Intensive insulin therapy† | 848 (63.2) | 828 (63.6) | 20 (50.0) | 0.070 |
| Basal insulin only | 171 (12.8) | 166 (12.8) | 5 (12.5) | |
| Split mixed insulin | 154 (11.5) | 144 (11.1) | 10 (25.0) | |

SD, standard deviation; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; DR, diabetic retinopathy; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid.
Data are presented as n, % unless otherwise specified.
*Severe DR (one or more of proliferative DR, clinically significant macular edema, prior laser photocoagulation or vitrectomy or vision loss).
†Multiple daily insulin injections or subcutaneous insulin pump therapy.
‡$p < 0.05$ (Welch's *t* test or Fisher's exact test).



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**Table 2—Multivariate analyses—factors independently associated with fibrate use**

| | Odds Ratio (95% CI) |
|---|---|
| Dyslipidemia (other than hypertriglyceridemia) | 3.53 (1.26–13.48)* |
| Type 2 diabetes | 3.30 (1.03–12.57)* |
| ACE-I/ARB use | 2.79 (1.17–8.05)* |
| Serum triglyceride (per mmol/L) | 1.36 (1.11–1.64)* |
| Severe DR†,‡ | 0.47 (0.22–0.95)* |
| DR or macular edema not otherwise specified† | 0.41 (0.16–0.96)* |
| Male sex | 1.07 (0.56–2.08) |
| Age (per year) | 1.01 (0.98–1.04) |
| Duration of diabetes (per year) | 1.01 (0.98–1.04) |
| HbA1C (per %) | 1.02 (0.75–1.06) |
| Serum LDL cholesterol (per mmol/L) | 0.80 (0.50–1.23) |
| ASA use | 0.59 (0.30–1.15) |
| Statin use | 0.45 (0.20–1.07) |

CI, confidence interval; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DR, diabetic retinopathy; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein; ASA, acetylsalicylic acid.
*$p < 0.05$.
†Versus nonproliferative diabetic retinopathy (reference).
‡Severe DR (one or more of proliferative DR, clinically significant macular edema, prior laser photocoagulation, vitrectomy or vision loss).

approach to minimize effect of bias caused by the rarity of fibrate use with a 5% level of significance. Statistical analyses were performed using SAS software, Version 9.4 (SAS Institute, Inc., Cary, NC). The study was approved by the Western University Health Sciences Research Ethics Board.

Of 24,736 patients, 1532 (6.2%) had DR, including 589 (43.9%) with severe DR. Of the 1532, 46 (3.0%) were on a fibrate. Patient characteristics are in Table 1. Factors predictive of fibrate use are in Table 2.

To our knowledge, this is the first study examining fibrate use in DR. This study's strength is the inclusion of detailed real-world clinical data of patients with a full range of DR severity, though as a cross-sectional study, it is limited by potential misclassification and ascertainment biases caused by reliance on self-reported fibrate use. Other limitations are: assessment of current (vs ever) fibrate use, absence of indication for fibrate (dyslipidemia or DR), and absence of formal validation of DR (likely contributing to fewer than expected patients with DR). We attempted to minimize selection bias by including all eligible adults with DR in WebDR, though the single-centre design precludes generalizability.

Despite strong evidence supporting fenofibrate to delay DR progression, fibrate use in DR at our centre is extremely low. This observation, if widely confirmed elsewhere, highlights an important care gap in DR management that should be addressed.

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## Footnotes and Disclosure

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