Predicting the Effect of Fenofibrate on Cardiovascular Risk for Individual Patients With Type 2 Diabetes

Charlotte Koopal,[1] Frank L.J. Visseren,[1] Jan Westerink,[1] Yolanda van der Graaf,[2] Henry N. Ginsberg,[3] and Anthony C. Keech[4]

Diabetes Care 2018;41:1244–1250 | https://doi.org/10.2337/dc17-0968

OBJECTIVE

In clinical trials, treatment with fenofibrate did not reduce the incidence of major cardiovascular events (MCVE) in patients with type 2 diabetes mellitus (T2DM). However, treatment effects reported by trials comprise patients who respond poorly and patients who respond well to fenofibrate. Our aim was to use statistical modeling to estimate the expected treatment effect of fenofibrate for individual patients with T2DM.

RESEARCH DESIGN AND METHODS

To estimate individual risk, the FIELD risk model, with 5-year MCVE as primary outcome, was externally validated in T2DM patients from ACCORD and the SMART observational cohort. Fenofibrate treatment effect was estimated in 17,142 T2DM patients from FIELD, ACCORD, and SMART. Individual treatment effect, expressed as absolute risk reduction (ARR), is the difference between treated and untreated MCVE risk. Results were stratified for patients with and without dyslipidemia (i.e., high triglycerides and low LDL cholesterol).

RESULTS

External validation of the FIELD risk model showed good calibration and moderate discrimination in ACCORD (C-statistic 0.67 [95% CI 0.65–0.69]) and SMART (C-statistic 0.66 [95% CI 0.63–0.69]). Median 5-year MCVE risk in all three studies combined was 6.7% (interquartile range [IQR] 4.0–11.7) in patients without (*N* = 13,224) and 9.4% (IQR 5.4–16.1%) in patients with (*N* = 3,918) dyslipidemia. The median ARR was 2.15% (IQR 1.23–3.68) in patients with dyslipidemia, corresponding with a number needed to treat (NNT) of 47, and 0.22% (IQR 0.13–0.38) in patients without dyslipidemia (NNT 455).

CONCLUSIONS

In individual patients with T2DM, there is a wide range of absolute treatment effect of fenofibrate, and overall the fenofibrate treatment effect was larger in patients with dyslipidemia. The method of individualized treatment effect prediction of fenofibrate on MCVE risk reduction in T2DM can be used to guide clinical decision making.

Patients with type 2 diabetes mellitus (T2DM) have a high risk of cardiovascular disease (CVD) (1). Although statins reduce cardiovascular morbidity and mortality significantly by reducing LDL cholesterol (LDL-C), the remaining residual risk underscores the clinical need for additional treatment options (2,3). Fibrates specifically target the dyslipidemia

[1]Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands
[2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
[3]Irving Institute for Clinical and Translational Research, Columbia College of Physicians and Surgeons, New York, NY
[4]National Health and Medical Research Council Clinical Trials Centre, Sydney Medical School, University of Sydney, Sydney, Australia

Corresponding author: Frank L.J. Visseren, f.l.j.visseren@umcutrecht.nl.

Received 26 May 2017 and accepted 26 January 2018.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-0968/-/DC1.

© 2018 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at http://www.diabetesjournals.org/content/license.

Downloaded from http://diabetesjournals.org/care/article-pdf/41/6/1244/553455/dc170968.pdf by guest on 01 June 2023

seen in T2DM by reducing plasma triglycerides (TG) by 30% and increasing HDL cholesterol (HDL-C) by 10% (4). The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, both placebo-controlled randomized clinical trials, investigated the effect of fenofibrate in patients with T2DM and showed no overall reduction in CVD (5,6). However, although the benefit of fenofibrate was not statistically significant, it is conceivable that there are patients in whom fenofibrate does convey clinical benefit (3). Subgroup analyses are a method frequently used to address this issue. Based on subgroup analysis in FIELD and ACCORD, the American Diabetes Association guideline recommends statin/fibrate combination therapy in T2DM in men with TG >2.3 mmol/L and HDL-C <0.9 mmol/L (7).

Individualized treatment effect prediction considers both favorable and unfavorable risk factors simultaneously and takes relative effects presented by randomized trials one step further by expressing treatment effect in terms of absolute risk reduction (ARR) for individual patients (8–13).

The aim of the current study was to estimate individual treatment effect of fenofibrate on major cardiovascular events (MCVEs) for T2DM patients from the FIELD and ACCORD randomized clinical trials and the Second Manifestations of ARTerial disease (SMART) observational cohort study.

RESEARCH DESIGN AND METHODS

FIELD, ACCORD, and SMART

FIELD evaluated the effect of fenofibrate compared with placebo in 9,795 patients with T2DM between the age of 50 and 75 years who were not taking statin therapy at study entry. Detailed information about the study design has previously been published (3). The primary outcomes were coronary events (coronary disease mortality and nonfatal myocardial infarction), which occurred in 544 patients during a 5-year median follow-up. FIELD reported an 11% reduction in coronary events in patients using fenofibrate (hazard ratio [HR] 0.89 [95% CI 0.75–1.05]) (5). In total, 859 patients suffered an MCVE, defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular mortality.

The ACCORD lipid trial consisted of 5,518 patients with T2DM and investigated the effect of fenofibrate in combination with atorvastatin compared with atorvastatin plus placebo (6,14). The primary outcome was MCVE, which occurred 601 times after a median follow-up of 4.7 years. The ACCORD trial reported an 8% reduction in MCVEs (i.e., nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) (HR 0.92 [95% CI 0.79–1.08]) in patients using fenofibrate on a background of statin therapy.

Although the primary end points used in FIELD and ACCORD differed, we used the MCVE composite end point for the analyses in the current study.

The SMART study is an ongoing longitudinal cohort study that started in 1996 and included 1,829 T2DM patients with and without CVD (15). In the SMART cohort, the composite end point MCVE was observed in 334 patients, with a median follow-up time of 5.8 years. In all three studies, written informed consent was obtained from all participants and the ethics boards of the institutions approved the studies.

Missing Data

In FIELD, 0.2% of data were missing for duration of T2DM and 0.3% for urinary albumin-to-creatinine ratio (UACR). In ACCORD, missing data ranged from 0.1% for current smoking to 4.3% in UACR. In SMART, missing data ranged from 0.05% for TG and HDL-C to 7% for UACR. Single imputation by bootstrapping and predictive mean matching was used (aregImpute in R, Hmisc package) to account for missing data in the predictors (16).

Model Derivation and Validation

For development of the FIELD model for the prediction of 5-year ARR for MCVE by fenofibrate, Cox proportional hazards models for time to MCVE were used, with time to event in years. For prevention of overfitting, predictors were prespecified based on the presence in three or more CVD prediction models for patients with T2DM (17). The initial model included the following variables at baseline: fenofibrate treatment, age, sex, ethnicity, diabetes duration, current smoking, previous CVD, use of antihypertensive medication, HbA_{1c}, systolic blood pressure, non–HDL-C, HDL-C, TG, UACR, dyslipidemia, estimated glomerular filtration rate (eGFR) (MDRD formula), and interaction terms between these predictors and fenofibrate. Metabolic syndrome was not added as a separate categorical variable because its individual components were included as single predictors. In eight of the nine prognostic models that were used for predictor selection, a marker for body weight was initially included but fell out of the model owing to inadequate (additional) prognostic value. Therefore, we did not add BMI or waist circumference to our set of predictors. Fenofibrate use was forced in the model. Model selection was based on backward selection using the Wald χ^2 statistic for removal of variables, based on which ethnicity, TG, and dyslipidemia dropped out of the model. TG probably fell out of the model because their prognostic value is already captured in non–HDL-C, which is a stronger predictor for CVD. Continuous variables were checked for nonnormality by visual inspection of the Martingale residual distribution, which led to log transformation of UACR and HDL-C. The Cox proportional hazards assumption was tested and met for all predictors. The final model is shown in Supplementary Box 1.

Model validation was performed in the ACCORD lipid trial and the SMART observational cohort study. To ensure adequate risk stratification, we recalibrated the final model for baseline survival in ACCORD and SMART to take differences in baseline survival (e.g., by a difference in background lipid-lowering therapy) into account. Model performance was tested with calculation of the C-statistic for discrimination and with calibration plots for predicted versus observed MCVE risk (expressed as event-free survival). For comparison, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) risk model (18) was validated in these three data sets (Supplementary Data).

Individualized Treatment Effect Prediction

For demonstration of the application of the prediction model in a large and heterogeneous group of patients that resembles clinical practice, patient data from FIELD, ACCORD, and SMART were combined (N = 17,142). Results were stratified for the presence of dyslipidemia, which was defined as TG >2.3 mmol/L and HDL-C <1.00 mmol/L for men and <1.30 mmol/L for women. Results stratified for TG ≤2.3 mmol/L and >2.3 mmol/L are shown in Supplementary Data. First, 5-year MCVE risk was calculated by setting treatment status to zero in the FIELD

Downloaded from http://diabetesjournals.org/care/article-pdf/41/6/1244/553455/dc170968.pdf by guest on 01 June 2023

risk model for all patients (irrespective of their actual treatment status). Second, ARR was calculated as MCVE risk minus on-treatment risk. ARR (%) was also expressed as number needed to treat (NNT = 100/ARR). An example of how ARR is calculated can be found in Supplementary Box 2. Subgroup-specific HRs for the effect of fenofibrate on 5-year MCVE risk in patients with and without dyslipidemia were derived from the combined FIELD and ACCORD data using Cox proportional hazards models. These were HR 0.97 (95% CI 0.86–1.09) for patients without dyslipidemia and HR 0.77 (95% CI 0.64–0.94) for patients with dyslipidemia. On-treatment risk was calculated by multiplying 5-year MCVE risk with the subgroup-specific HR for patients with and without dyslipidemia. Third, patients were stratified according to treatment effect. The analyses were performed in R, version 3.2.2 (package 'rms'; R Core Team, Vienna, Austria), and SAS, version 9.3. Fourth, a calculation sheet was made (Microsoft Office Excel 2007).

RESULTS

Baseline Characteristics

FIELD included 9,795 patients, ACCORD 5,518 patients, and SMART 1,829 patients with T2DM. The mean age was 62.2 ± 7.3 years in the total population, and 66% were men (Table 1). Of the FIELD participants, 22% had a history of CVD and the median duration of T2DM was 5 years (interquartile range [IQR] 2–10). In ACCORD, 37% of the patients had a history of CVD with a median duration of T2DM of 9 years (IQR 5–15). In SMART, 66% had a history of CVD and the median T2DM duration was 10 years (IQR 5–15 years).

External Validation of the Prediction Model

The FIELD risk model for the 5-year treatment effect of fenofibrate on MCVE in patients with T2DM is provided in Supplementary Box 1. External validation showed moderate discrimination, with a C-statistic of 0.67 (95% CI 0.65–0.69) and 0.68 (95% 0.64–0.72) in ACCORD and SMART, respectively. Calibration between observed and predicted 5-year MCVE risk was well balanced in both studies (Fig. 1). The ADVANCE risk model was less well calibrated and had a lower C-statistic in ACCORD and SMART compared with the FIELD risk model (Supplementary Figs. 1–3).

Five-Year MCVE-Risk and Treatment Effect of Fenofibrate

In a pooled analysis of FIELD, ACCORD, and SMART, the median 5-year MCVE risk was 9.4% (IQR 5.4–16.2) and 6.7% (IQR 4.0–11.7) in patients with and patients without dyslipidemia, respectively (Fig. 2). There was a wide range in absolute treatment effect of fenofibrate, with a median ARR of 2.15% (IQR 1.24–3.69, NNT 47) in patients with dyslipidemia and 0.22% (IQR 0.13–0.38, NNT = 455) in patients without dyslipidemia (Fig. 2). Results were similar when stratified for TG ≤2.3 mmol/L and >2.3 mmol/L (Tables 1 and 2 and Supplementary Figs. 4 and 5). For calculation of individual ARR, a calculation sheet is provided in Supplementary Data.

Of patients with dyslipidemia, 54% had an ARR ≥2% (NNT ≤50). Patients with dyslipidemia and an ARR ≥2% (NNT ≤50) and had a median MCVE risk of 15.4% (IQR 11.7–22.5) and a median ARR of 3.52% (IQR 2.37–5.13) (Table 2). In patients with dyslipidemia and ARR <2%, the median MCVE risk was 5.2% (IQR 3.8–6.8) and the median ARR was 1.18% (0.86–1.55). Of patients with dyslipidemia, 16% (*N* = 634) had an ARR <1.0%. The median MCVE risk in these patients was 3.26% (IQR 2.63–3.90) and median ARR 0.74% (IQR 0.60–0.89, NNT = 135).

Of patients without dyslipidemia, 97% had ARR by fenofibrate of <1% (NNT >100). In these patients, the median MCVE risk was 6.6% (IQR 3.9–11.2) and

Table 1—Baseline characteristics

	FIELD	ACCORD	SMART	Total
N	9,795	5,518	1,829	17,142
Age (years)	62.2 ± 6.9	62.8 ± 6.6	60.3 ± 10.2	62.2 ± 7.3
Male sex	63 (6,138)	69 (3,824)	70 (1,272)	66 (11,234)
Duration of T2DM (years)	5 (2–10)	9 (5–15)	4 (1–9)	6 (3–11)
Previous CVD	22 (2,131)	37 (2,016)	69 (1,260)	32 (5,407)
Current smoking	9 (922)	15 (803)	25 (456)	13 (2,181)
Antihypertensive medication	58 (5,659)	82 (4,530)	62 (1,130)	66 (11,319)
Systolic blood pressure (mmHg)	140 ± 15	134 ± 17	145 ± 21	139 ± 17
Diastolic blood pressure (mmHg)	82 ± 9	74 ± 10	83 ± 12	79 ± 10
BMI (kg/m^2)	30.7 ± 5.5	32.3 ± 5.3	29.0 ± 5.0	31.0 ± 5.5
Waist circumference (cm)	104 ± 13	108 ± 14	101 ± 13	105 ± 13
Total cholesterol (mmol/L)	5.0 ± 0.7	4.5 ± 1.0	4.8 ± 1.4	4.9 ± 0.9
HDL-C (mmol/L)	1.10 ± 0.26	0.99 ± 0.20	1.13 ± 0.33	1.06 ± 0.26
Non–HDL-C (mmol/L)	3.9 ± 0.7	3.5 ± 1.0	3.7 ± 1.4	3.9 ± 0.9
TG (mmol/L)	1.73 (1.34–2.32)	1.82 (1.28–2.59)	1.7 (1.2–2.5)	1.75 (1.30–2.42)
LDL-C (mmol/L)	3.1 ± 0.7	2.6 ± 0.8	2.8 ± 1.1	2.9 ± 0.8
HbA_{1c} (%)	6.9 (6.1–7.8)	8.1 (7.6–8.8)	6.8 (6.2–7.7)	7.4 (6.5–8.3)
HbA_{1c} (mmol/mol)	52 (43–62)	65 (60–73)	51 (44–61)	57 (48–67)
Glucose (mmol/L)	8.91 ± 2.60	9.71 ± 2.90	8.71 ± 2.92	9.15 ± 2.76
eGFR (mL/min/1.73 m^2)	88 ± 18	90 ± 22	78 ± 22	87 ± 20
UACR (mg/mmol)	1.10 (0.60–2.95)	1.58 (0.79–5.20)	1.43 (0.85–3.06)	1.25 (0.68–3.50)

Data are mean ± SD, median (IQR), or % (*N*) unless otherwise indicated. eGFR calculated with the MDRD formula.

Downloaded from http://diabetesjournals.org/care/article-pdf/41/6/1244/553455/dc170968.pdf by guest on 01 June 2023

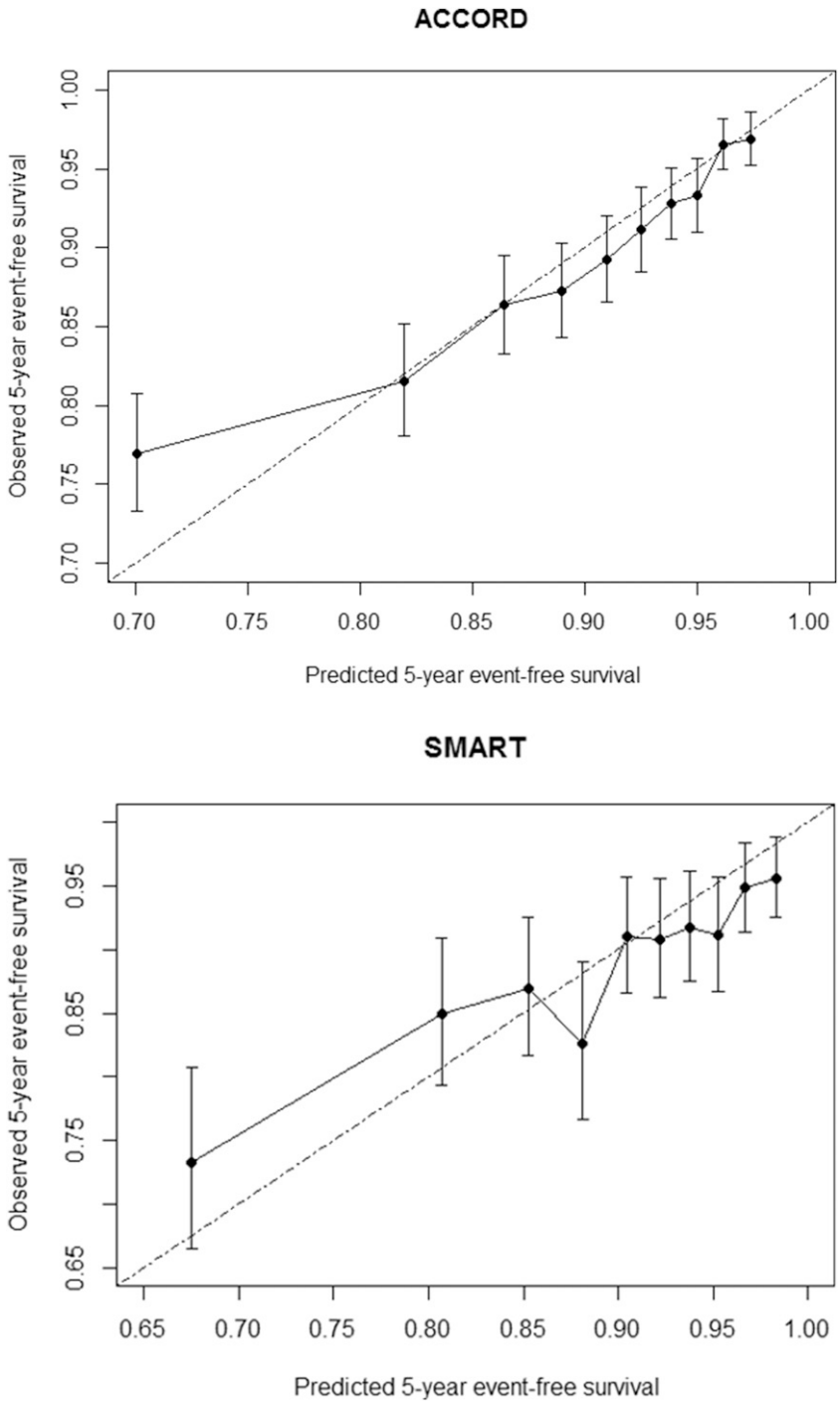

Figure 1—External calibration of the FIELD risk score in the ACCORD and SMART studies. Calibration of observed vs. predicted 5-year event-free survival for MCVE within deciles of predicted risk.

ARR 0.21% (IQR 0.13–0.36) (Table 2). The median MCVE risk in patients without dyslipidemia with an ARR ≥1% (NNT ≤100) was 36.8% (IQR 33.6–42.9).

CONCLUSIONS

In this study, we used statistical modeling to estimate the individual treatment effect of fenofibrate for 17,142 patients with T2DM from the FIELD and ACCORD randomized trials and the SMART observational cohort study. We found a wide range of individual treatment effects. More than half (54%) of the patients with dyslipidemia had a substantial treatment effect (ARR >2%, NNT <50) and nearly all (97%) patients without dyslipidemia had a small treatment effect (<1%, NNT >100).

Individualized treatment prediction is a method to overcome disadvantages of subgroup analyses and facilitate the translation from randomized clinical trials to individual patients (8–13).

Subgroup analyses often overestimate treatment effect (19) and study only one patient characteristic at the time (17), thereby not taking into account that treatment effect usually depends on several, often correlated, patient characteristics. This can lead to confounded interpretations (20). Individualized treatment prediction uses multivariate models to estimate individual, absolute treatment effects, thereby contributing to the improvement of personalized medicine.

As mentioned before, patients with T2DM have a high residual cardiovascular risk, even when risk factors are adequately treated according to guidelines (2), and additional treatment options to reduce cardiovascular risk are needed (3). On the other hand, overtreatment is undesirable, especially in T2DM patients who usually use many medications including oral hyperglycemic drugs and/or insulin. Before adding additional drugs, such as fenofibrate, both physician and patient need to know what the expected effect of fenofibrate will be. The multivariable prediction model presented in this article can be used to translate group-level evidence to individual patients in clinical practice. Presenting an individual treatment effect can benefit communication with a patient because benefits can be weighed against expected harms such as costs and side effects. This will facilitate shared decision making and improve treatment adherence (21,22). Although the use of individualized treatment effect prediction in clinical practice might seem complicated, we provide an easy-to-use calculation sheet that only requires a physician to fill in the patient's clinical information. This way physicians are able to practice evidence-based personalized medicine in daily practice.

External validation of the FIELD risk model showed good calibration and moderate discrimination in both the ACCORD randomized clinical trial and in "real-life patients" from the SMART observational cohort study after recalibration of baseline survival. This means that the FIELD risk model can be used to estimate 5-year MCVE risk for individual patients with T2DM. For individualized treatment effect prediction, it is especially important that the predicted risks are in agreement with the observed risks, and therefore

Downloaded from http://diabetesjournals.org/care/article-pdf/41/6/1244/553455/dc170968.pdf by guest on 01 June 2023

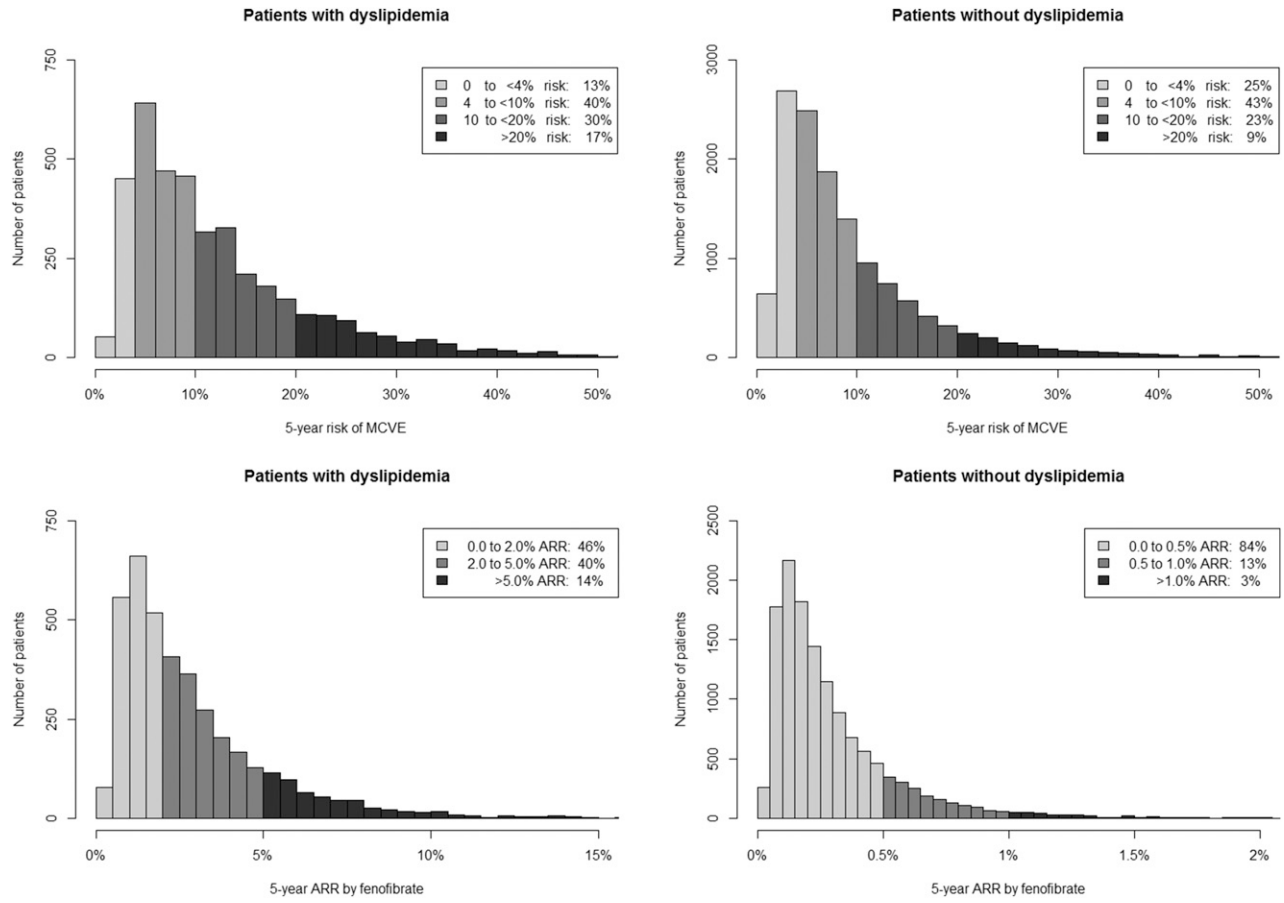

Figure 2—Top: Distribution of predicted 5-year MCVE risk in T2DM patients with and T2DM patients without dyslipidemia. Bottom: Distribution of individual treatment effect of fenofibrate on MCVE risk in T2DM patients with and T2DM patients without dyslipidemia. Treatment effect is expressed as ARR.

calibration is the most important performance measure in this regard (10). One of the reasons that there was a difference in baseline survival might be the fact that FIELD patients were not on background therapy with statins. However, the well-balanced calibration of the FIELD model in ACCORD after baseline risk adjustment indicates that the difference in background statin therapy did not influence treatment effect predictions.

We found that, overall, patients with dyslipidemia had a larger treatment effect of fenofibrate than patients without dyslipidemia. This is due to a larger relative treatment effect, which is in line with two meta-analyses that found a higher relative benefit of fibrate in patients with dyslipidemia (23,24). Furthermore, patients with dyslipidemia generally have a higher 5-year MCVE risk than patients without dyslipidemia because both low HDL-C and high TG levels are independently related to increased CVD risk (25–27). That fenofibrate did not show an overall treatment effect in FIELD and ACCORD is probably because the majority of patients did not have dyslipidemia at baseline. Although we generally found a higher treatment effect in patients with dyslipidemia, we also found that some patients without dyslipidemia had a considerable fenofibrate treatment effect (ARR $\geq$1%, NNT $<$100). Furthermore, 16% of patients with dyslipidemia had a small treatment effect (ARR $<$1%, NNT $>$100). These results indicate that simply treating all patients with dyslipidemia and none without dyslipidemia with fenofibrate does not necessarily tailor the right treatment to the right patient. Therefore, treatment recommendations should go beyond group level and use individualized treatment effect prediction to guide clinical decision making.

Future projects to develop this method and add to the development of personalized medicine should be aimed at estimating the combined effect of different types of medication, e.g., glycemic control, statins, and blood pressure–lowering medication, on clinical end points because the combined effect of these medications might be different than each effect separately. For development of a model like this, trials that investigate the combined effect of these medications should be performed. Furthermore, the effect on microvascular T2DM end point such as nephropathy or retinopathy can be estimated, just like quality of life. A recent development is to predict gain in healthy life expectancy instead of risk because risk is in very large part determined by age (3). Another interesting future project would be to determine which lipid effect of fenofibrate (TG lowering, HDL increasing, or other) is most important for the observed treatment effect. Finally, as clinical practice changes over time, it would be valuable to validate and update the presented model regularly.

Some limitations with regard to this study should be considered. First, the prediction model presented here was developed using data from clinical trials, which might limit generalizability to patients

Downloaded from http://diabetesjournals.org/care/article-pdf/41/6/1244/553455/dc170968.pdf by guest on 01 June 2023

Table 2—Patient characteristics according to treatment effect in T2DM patients with and without dyslipidemia

	No dyslipidemia (*N* = 13,224)		Dyslipidemia (*N* = 3,918)	
	ARR <1.0%	ARR ≥1.0%	ARR <2.0%	ARR ≥2.0%
N	12,891	333	1,814	2,104
5-year MCVE risk (%)	6.6 (3.9–11.2)	36.9 (33.5–42.6)	5.2 (3.8–6.9)	15.4 (11.7–22.5)
ARR (%)	0.21 (0.13–0.36)	1.19 (1.08–1.38)	1.18 (0.87–1.56)	3.51 (2.66–5.13)
Age (years)	62.3 ± 7.2	70.1 ± 5.8	58.4 ± 6.3	63.7 ± 6.9
Male sex	66 (8,543)	93 (308)	45 (814)	75 (1,569)
Duration of T2DM (years)	6 (2–11)	14 (7–21)	4 (2–8)	8 (4–13)
Previous CVD	29 (3,765)	95 (316)	9 (162)	55 (1,164)
Current smoking	11 (1,458)	36 (120)	8 (144)	22 (459)
Antihypertensive medication	64 (8,244)	91 (302)	58 (1,052)	82 (1,721)
Systolic blood pressure (mmHg)	139 ± 17	153 ± 19	134 ± 15	142 ± 18
Diastolic blood pressure (mmHg)	80 ± 10	77 ± 13	80 ± 9	79 ± 11
BMI (kg/m^2)	30.7 ± 5.6	29.2 ± 4.4	32.5 ± 5.5	31.8 ± 5.1
Waist circumference (cm)	104 ± 14	105 ± 13	106 ± 13	108 ± 13
Total cholesterol (mmol/L)	4.8 ± 0.9	4.9 ± 1.0	5.1 ± 0.9	5.2 ± 1.1
HDL-C (mmol/L)	1.12 ± 0.26	0.95 ± 0.18	0.93 ± 0.16	0.84 ± 0.14
Non-HDL-C (mmol/L)	3.7 ± 0.8	3.9 ± 1.0	4.2 ± 0.8	4.3 ± 1.0
TG (mmol/L)	1.54 (1.21–1.92)	1.70 (1.35–2.07)	2.90 (2.55–3.47)	3.10 (2.61–3.90)
LDL-C (mmol/L)	2.9 ± 0.8	3.1 ± 0.9	2.7 ± 0.8	2.8 ± 0.9
HbA_{1c} (%)	7.3 (6.4–8.2)	8.3 (7.5–9.3)	7.2 (6.3–8.1)	8.0 (7.2–8.9)
HbA_{1c} (mmol/mol)	56 (46–66)	67 (58–78)	55 (45–65)	64 (55–74)
Glucose (mmol/L)	8.93 ± 2.68	9.98 ± 3.06	9.15 ± 2.59	10.31 ± 3.02
eGFR (mL/min/1.73 m^2)	88 ± 20	72 ± 18	92 ± 20	82 ± 22
UACR (mg/mmol)	1.15 (0.65–2.92)	11.75 (4.40–49.60)	1.01 (0.60–2.03)	2.70 (1.13–10.38)

Numbers are mean ± SD, median (IQR), or % (*N*) unless otherwise indicated. eGFR calculated with the MDRD formula.

with T2DM in clinical practice because clinical trial patients tend to have less comorbidity, better adherence, and a larger expected treatment benefit (28). However, validation of the FIELD risk model in the SMART observational cohort showed good risk calibration, indicating that generalization to real-life patients is probably fairly accurate. Furthermore, by using pooled data from FIELD, ACCORD, and SMART, we created a large and heterogeneous group of T2DM patients that resembles the wide variety of patients seen in clinical practice. Also, in FIELD there was a 23% statin drop-in rate; however, a calibration plot showed a good balance between predicted and observed risks in FIELD, indicating that the statin drop-in did not influence the precision of the predictions made at baseline (Supplementary Data). Second, the cutoffs for TG and HDL-C to define dyslipidemia have not been generally established. We used sex-specific HDL-C cutoffs (HDL-C <1.00 mmol/L for men and <1.30 mmol/L for women) as in the definition for metabolic syndrome (29) and as used in FIELD (5) and a TG cutoff of >2.3 mmol/L based on the definition for moderately increased TG of the 2012 Endocrine Society guideline (30), as well as the 2016 ESC/EAS (European Society of Cardiology and European Atherosclerosis Society) guidelines that recommend considering lipid-lowering treatment when TG levels are >2.3 mmol/L (31). The two meta-analyses that investigated the effect of fibrates on CVD also used the TG cutoff of >2.3 mmol/L, but one used an HDL-C cutoff of <0.9 mmol/L, and the other of <1.0 mmol/L, to define dyslipidemia (23,24). These differences in dyslipidemia definition might complicate the generalizability of our results. Third, predictions are made for a 5-year period, while patients and physicians might want information for a longer period or even for over the lifetime. The 5-year time period was chosen owing to the available follow-up data in the derivation and validation sets, but longer-term predictions would have been of added value.

In conclusion, in individual patients with T2DM there is a wide range in the individual treatment effect of fenofibrate on MCVE risk. We found a wide range of individual treatment effect of fenofibrate in patients with T2DM, and overall, patients with dyslipidemia had a larger fenofibrate treatment effect than patients without dyslipidemia. The method of individualized treatment effect prediction of fenofibrate on MCVE risk reduction in T2DM can be used to guide clinical decision making.

Acknowledgments. The authors gratefully acknowledge the contribution of Rachel O'Connell, statistician at the National Health and Medical Research Council Clinical Trials Centre.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. C.K. researched data and wrote the manuscript. F.L.J.V. contributed to discussion and reviewed and edited the manuscript. J.W. reviewed and edited the manuscript. Y.v.d.G. contributed to the discussion and reviewed and edited the manuscript. H.N.G. reviewed and edited the manuscript. A.C.K. researched data, contributed to the discussion, and reviewed and edited the manuscript. F.L.J.V. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Diabetes mellitus: a major risk factor for cardiovascular disease. A joint editorial statement by the

Downloaded from http://diabetesjournals.org/care/article-pdf/41/6/1244/553455/dc170968.pdf by guest on 01 June 2023

American Diabetes Association; The National Heart, Lung, and Blood Institute; The Juvenile Diabetes Foundation International; The National Institute of Diabetes and Digestive and Kidney Diseases; and The American Heart Association. Circulation 1999; 100:1132–1133
2. Fruchart JC, Davignon J, Hermans MP, et al.; Residual Risk Reduction Initiative (R3i). Residual macrovascular risk in 2013: what have we learned? Cardiovasc Diabetol 2014;13:26
3. Tarantino N, Santoro F, De Gennaro L, et al. Fenofibrate/simvastatin fixed-dose combination in the treatment of mixed dyslipidemia: safety, efficacy, and place in therapy. Vasc Health Risk Manag 2017;13:29–41
4. Wierzbicki AS. Fibrates in the treatment of cardiovascular risk and atherogenic dyslipidaemia. Curr Opin Cardiol 2009;24:372–379
5. Keech A, Simes RJ, Barter P, et al.; FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–1861
6. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574
7. American Diabetes Association. Cardiovascular disease and risk management. Sec. 8. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016;39(Suppl. 1):S60–S71
8. Dorresteijn JA, Visseren FL, Ridker PM, et al. Aspirin for primary prevention of vascular events in women: individualized prediction of treatment effects. Eur Heart J 2011;32:2962–2969
9. Dorresteijn JA, Visseren FL, Ridker PM, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. BMJ 2011;343:d5888
10. van der Leeuw J, Ridker PM, van der Graaf Y, Visseren FL. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. Eur Heart J 2014;35:837–843
11. van der Leeuw J, Visseren FL, Woodward M, et al. Predicting the effects of blood pressure-lowering treatment on major cardiovascular events for individual patients with type 2 diabetes mellitus: results from Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation. Hypertension 2014;65:115–121
12. Dorresteijn JA, Boekholdt SM, van der Graaf Y, et al. High-dose statin therapy in patients with stable coronary artery disease: treating the right patients based on individualized prediction of treatment effect. Circulation 2013;127:2485–2493
13. van Kruijsdijk RC, Visseren FL, Ridker PM, et al. Individualised prediction of alternate-day aspirin treatment effects on the combined risk of cancer, cardiovascular disease and gastrointestinal bleeding in healthy women. Heart 2015; 101:369–376
14. Buse JB, Bigger JT, Byington RP, et al.; ACCORD Study Group. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol 2007;99:21i–33i
15. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second Manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol 1999;15:773–781
16. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006; 59:1087–1091
17. Hayward RA, Kent DM, Vijan S, Hofer TP. Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. BMC Med Res Methodol 2006;6:18
18. Kengne AP, Patel A, Marre M, et al. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. Eur J Cardiovasc Prev Rehabil 2011;18:393–398
19. Tanniou J, Tweel IV, Teerenstra S, Roes KC. Level of evidence for promising subgroup findings in an overall non-significant trial. Stat Methods Med Res 2014;25:2193–2213
20. Varadhan R, Wang SJ. Standardization for subgroup analysis in randomized controlled trials. J Biopharm Stat 2014;24:154–167
21. Weymiller AJ, Montori VM, Jones LA, et al. Helping patients with type 2 diabetes mellitus make treatment decisions: statin choice randomized trial. Arch Intern Med 2007;167:1076–1082
22. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. JAMA 2002;288: 2868–2879
23. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. Atherosclerosis 2011;217:492–498
24. Bruckert E, Labreuche J, Deplanque D, Touboul PJ, Amarenco P. Fibrates effect on cardiovascular risk is greater in patients with high triglyceride levels or atherogenic dyslipidemia profile: a systematic review and meta-analysis. J Cardiovasc Pharmacol 2011;57:267–272
25. Di Angelantonio E, Gao P, Pennells L, et al.; Emerging Risk Factors Collaboration. Lipid-related markers and cardiovascular disease prediction. JAMA 2012;307:2499–2506
26. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet 2014;384: 626–635
27. Sarwar N, Sandhu MS, Ricketts SL, et al.; Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies [published correction appears in Lancet 2010;376:90]. Lancet 2010;375:1634–1639
28. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" Lancet 2005;365:82–93
29. Grundy SM, Cleeman JI, Daniels SR, et al.; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–2752
30. Berglund L, Brunzell JD, Goldberg AC, et al.; Endocrine Society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97:2969–2989
31. Catapano AL, Graham I, De Backer G, et al.; Authors/Task Force Members. 2016 ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 2016;253:281–344

Downloaded from http://diabetesjournals.org/care/article-pdf/41/6/1244/553455/dc170968.pdf by guest on 01 June 2023