Risk of Anemia With Metformin Use in Type 2 Diabetes: A MASTERMIND Study

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OBJECTIVE

To evaluate the association between metformin use and anemia risk in type 2 diabetes, and the time-course for this, in a randomized controlled trial (RCT) and real-world population data.

RESEARCH DESIGN AND METHODS

Anemia was defined as a hemoglobin measure of <11 g/dL. In the RCTs A Diabetes Outcome Progression Trial (ADOPT; $n = 3,967$) and UK Prospective Diabetes Study (UKPDS; $n = 1,473$), logistic regression was used to model anemia risk and nonlinear mixed models for change in hematological parameters. In the observational Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) population ($n = 3,485$), discrete-time failure analysis was used to model the effect of cumulative metformin exposure on anemia risk.

RESULTS

In ADOPT, compared with sulfonylureas, the odds ratio (OR) (95% CI) for anemia was 1.93 (1.10, 3.38) for metformin and 4.18 (2.50, 7.00) for thiazolidinediones. In UKPDS, compared with diet, the OR (95% CI) was 3.40 (1.98, 5.83) for metformin, 0.96 (0.57, 1.62) for sulfonylureas, and 1.08 (0.62, 1.87) for insulin. In ADOPT, hemoglobin and hematocrit dropped after metformin initiation by 6 months, with no further decrease after 3 years. In UKPDS, hemoglobin fell by 3 years in the metformin group compared with other treatments. At years 6 and 9, hemoglobin was reduced in all treatment groups, with no greater difference seen in the metformin group. In GoDARTS, each 1 g/day of metformin use was associated with a 2% higher annual risk of anemia.

CONCLUSIONS

Metformin use is associated with early risk of anemia in individuals with type 2 diabetes, a finding consistent across two RCTs and replicated in one real-world study. The mechanism for this early fall in hemoglobin is uncertain, but given the time course, is unlikely to be due to vitamin B_{12} deficiency alone.

Anemia is a common finding in individuals with type 2 diabetes (1). Metformin is the first-line therapy for treatment of type 2 diabetes in most individuals and the most widely prescribed oral antidiabetic medication. A recent meta-analysis reviewed all available studies on associations between metformin use and vitamin B_{12} levels, anemia, and neuropathy in individuals with type 2 diabetes (2). The meta-analysis confirmed individuals taking metformin had a significantly higher risk of vitamin B_{12} deficiency than those not taking metformin and significantly lower serum B_{12}

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concentrations, which depended on dose and duration of treatment. Although this meta-analysis reported no association between metformin use and anemia risk, it is important to note that there were only four eligible studies, and most of these were cross-sectional or case-control, which did not have anemia as their primary end point (3–6). In contrast, the Diabetes Prevention Program (DPP) Outcomes Study showed metformin use in individuals with impaired glucose tolerance was associated with an increased risk of anemia at 5 years, independent of vitamin B_{12} status (7). There is therefore uncertainty about whether metformin causes anemia and whether or not this is mediated by B_{12} deficiency in metformin-treated individuals with type 2 diabetes.

The aims of this study were firstly to use randomized controlled trial (RCT) data with repeated hematological measures to determine whether there is an association between metformin use and anemia risk in type 2 diabetes, and, if so, what is the time frame for this? Secondly, to quantify risk in a real-world setting by examining whether cumulative exposure to metformin is associated with an increase in the incidence of anemia using routinely collected clinical data.

RESEARCH DESIGN AND METHODS

Data Sources

Three data sets were analyzed: two from RCTs, A Diabetes Outcome Progression Trial (ADOPT) and the UK Prospective Diabetes Study (UKPDS), and one from routine clinical data of Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS).

- ADOPT was a trial in which 4,351 drug-naive individuals recently diagnosed with type 2 diabetes were assigned randomly to thiazolidinediones (TZDs), metformin, or sulfonylurea monotherapy and monitored for 5 years (8). Hematological measures were collected at baseline, 6 months, 1 year, and annually thereafter.
- UKPDS was a trial in which 4,209 individuals with newly diagnosed type 2 diabetes were randomized to receive a conventional (diet) or intensive glycemic management strategy (insulin, sulfonylurea, or metformin) (9,10). Hematological measures were collected at baseline and at 3, 6, and 9 years of follow-up.
- GoDARTS is a large population-based cohort of ~10,000 individuals with type 2 diabetes, with comprehensive electronic medical records containing detailed information on all encashed prescriptions (including daily dose and adherence) from 1994 onward in Tayside and Fife, Scotland, as well as all routinely collected biochemistry and hematology measures (11).

Definition of Anemia

Hemoglobin (Hb) was the outcome variable. It was used as a continuous variable in ADOPT and UKPDS to investigate change over time and recoded as a binary outcome for estimating the risk of anemia in all three studies. The anemia end point was defined as the first Hb measure of $<$11 g/dL in both men and women (the moderate anemia definition used by the World Health Organization) after diabetes diagnosis. Individuals with prevalent anemia at baseline (diagnosis) (defined by the World Health Organization as Hb of $<$12 g/dL in women and 13 g/dL in men) were excluded from this analysis.

Study Populations

ADOPT

All participants in the intention-to-treat subset were eligible for the study. Individuals with missing baseline covariates or anemia at baseline were excluded.

UKPDS

All participants with $>$120% ideal body weight in the 15 centers recruited before 1988 were eligible for the study (9). Individuals with missing baseline covariates or anemia at baseline were excluded.

GoDARTS

Individuals with type 2 diabetes diagnosed on or after 1 January 1996 were eligible for the study, thus ensuring sufficient prescribing information and Hb measurements. In addition, individuals were required to have a baseline Hb measure (defined as closest measure to type 2 diabetes diagnosis up to 1 year prior) and no anemia at baseline. The study period for eligible individuals was defined as time from type 2 diagnosis (baseline) until the first anemia event, death, leaving area, or end of follow-up (30 September 2015), whichever came first.

Statistical Analysis

ADOPT and UKPDS

The risk of moderate anemia at any time point during the trials was modeled using logistic regression. The reference groups for treatment were sulfonylureas for ADOPT and diet for UKPDS. Covariates included in the model were sex, baseline age, Hb, estimated glomerular filtration rate (eGFR), and BMI.

Hematological changes over time were modeled using nonlinear mixed models. Hb was modeled in ADOPT and UKPDS. Hematocrit (Hct) was modeled in ADOPT, and packed cell volume (PCV) was modeled in UKPDS as a proxy for Hct, which was not available. Hb adjusted for Hct (ADOPT) or PCV (UKPDS) was also modeled to assess whether these were temporally related. In addition, mean corpuscular volume (MCV) was modeled in ADOPT. Data are presented as plots of predictions of the fixed effects for each treatment.

GoDARTS

Discrete time survival analysis was used to evaluate the effects of cumulative drug exposure. This model is set up as a logistic regression in which each individual contributes one observation for each 28-day time interval during the study period. A data matrix was generated with one row for each individual under observation in each time interval and columns specifying event status (coded as binary), fixed, and time-dependent covariates at the start of each time interval.

Exposure to each diabetes drug class (metformin, sulfonylureas, insulin, TZDs, acarbose, glucagon-like peptide receptor agonist [GLP-1 RA], dipeptidyl peptidase 4 inhibitor [DPP4i], glinide, and sodium–glucose cotransporter 2 inhibitor [SGLT2i]) was calculated from the date and intended duration of each prescription, but gaps between prescriptions did not accumulate exposure; therefore, adherence was accounted for in the model. Cumulative exposure of each drug class was calculated as the sum of all earlier intervals. If the drug was discontinued during the study, the cumulative exposure was still carried forward to subsequent time intervals.

Age at diabetes diagnosis, sex, baseline Hb, calendar year of diabetes diagnosis, and social deprivation (coded as 1–5, with 1 most deprived and 5 least deprived) were included as fixed covariates. Time from diabetes diagnosis was included as a time-dependent covariate. In addition, we considered cumulative exposure to metformin in terms of total

dose. BMI and eGFR were included as time-dependent covariates in a subgroup of individuals with these data available.

Pharmacoepidemiological studies are prone to allocation bias. To be satisfied that an estimate of a drug's potential causal effect cannot be due to time invariant between-person confounding, we include two time-updated terms for each drug class: one for ever-exposure and one for cumulative exposure. We focus the inference of causality on the cumulative term (12). The terms for ever-exposure and cumulative exposure can be given a visual representation by plotting a regression line through the unadjusted rates of anemia grouped by cumulative metformin exposure, representing the linear effect of cumulative exposure. The difference between the data point for the unexposed time ($x = 0$) and the estimated regression line at this point gives the magnitude of the ever-exposed term. This is the sum of any immediate stepwise effect of metformin and any difference in prior anemia risk in the never-users versus ever-users of metformin.

GoDARTS analysis was conducted using SAS 9.4 software. ADOPT and UKPDS analyses were conducted using R software.

RESULTS

RCT Data Sets (ADOPT and UKPDS)

Study Populations and Anemia Rates

In ADOPT, from 4,127 individuals in the intention-to-treat population, 153 were anemic at baseline, and a further 7 had missing covariate data, leaving 3,967 individuals in the study population (mean [SD] Hb 14.5 [1.1] g/dL, age 56.6 [10.0] years, with 58.9% men). There were 1,343 metformin, 1,289 sulfonylurea, and 1,335 TZD users, with anemia event rates of 38 (2.8%), 19 (1.5%), and 76 (5.7%), respectively, over the 5-year follow-up period.

In UKPDS, from 1,704 individuals, 52 were anemic at baseline, and a further 179 had missing covariate data, leaving 1,473 individuals in the study population (mean [SD] Hb 15.1 [1.2] g/dL, age 52.8 [8.1] years, with 47.1% men). There were 300 metformin-, 461 sulfonylurea-, 360 insulin-, and 352 diet-treated individuals, with anemia event rates of 19 (6.3%), 5 (1.1%), 9 (2.5%), and 6 (1.7%), respectively, over the 9-year follow-up period.

Logistic Regression Model for Anemia Risk

The results of the logistic regression for risk of moderate anemia are presented in Supplementary Tables 1 and 2 for ADOPT and UKPDS respectively. In ADOPT, the adjusted odds ratio (OR) (95% CI), with sulfonylureas as the reference group, was 1.93 (1.10, 3.38) for metformin and 4.18 (2.50, 7.00) for TZDs. Other predictors of moderate anemia risk were older age, lower baseline Hb, and male sex.

In UKPDS, the adjusted OR (95% CI), with diet as the reference group, was 4.42 (2.28, 8.57) for metformin, 0.53 (0.19, 1.48) for sulfonylureas, and 1.79 (0.73, 4.42) for insulin. In addition, lower baseline Hb was a predictor of moderate anemia risk.

Nonlinear Mixed Model for Hb Change Over Time

The plots of the prediction of the fixed effects from the nonlinear mixed model for each treatment group over time are presented in Fig. 1.

In ADOPT, there was an immediate drop from baseline (by first measurement at 6 months) in Hb (Fig. 1*A*) in both the metformin and TZD arms. The effect was much larger with TZD treatment, but the metformin treatment arm followed a similar pattern. Hct fell in a similar pattern to that seen for Hb after both metformin and TZD treatment (Fig. 1*B*), and this reduction in Hct completely mediated the fall in Hb (Fig. 1*C*). There was no further Hb decrease in ADOPT between 3 and 5 years; at 5 years, mean Hb was 0.42 g/dL (95% CI 0.20, 0.65) lower in the metformin-treated arm than the sulfonylurea-treated arm. There was a significant downward linear trend in MCV over the 5 years in the metformin treatment arm ($P < 0.0001$) but no significant trend in the TZD or sulfonylurea arms (Supplementary Fig. 1).

In UKPDS, there was also a postbaseline reduction in Hb when first measured (at 3 years) in those randomized to metformin compared with all other treatments (Fig. 1*D*), with the Hb 0.49 g/dL (95% CI 0.41, 0.57) lower that those treated with diet. Hb fell in all treatment groups at years 6 and 9, but with no greater further fall seen in the metformin- versus diet-treated group (0.49 g/dL [−1.64, 2.62] vs. 0.50 g/dL [−1.71, 2.72] fall from 3 to 9 years). Similar to ADOPT, the PCV (proxy for Hct) also fell with metformin treatment (Fig. 1*E*), and adjustment for the fall in PCV largely ameliorated the fall in Hb (Fig. 1*F*).

Routine Clinical Data Set (GoDARTS)

Derivation of Study Population

From a total of 6,440 individuals, 3,765 (58%) had a baseline Hb measure. Of these, 280 were excluded because they were anemic at diagnosis, leaving 3,485 individuals for analysis. A comparison of characteristics of individuals included and excluded in the study is presented in Supplementary Table 3. Individuals excluded due to missing baseline Hb measure were younger, with a higher proportion of men. However, individuals excluded due to anemia at baseline were older, with a higher proportion of women. The final study population was older than the overall type 2 diabetes population (mean [SD] 62.7 (10.6) vs. 61.8 [11.0] years at diagnosis, respectively; $P = 0.0005$), with no difference in proportion of men and women (55.5% men in the final study population) and mean Hb 14.7 (SD 1.2) g/dL.

Comparison of Exposed and Unexposed Individuals

Of the 3,485 individuals in the study, 2,487 had accumulated some exposure to metformin by the end of follow-up. Table 1 shows the comparison of characteristics at diabetes diagnosis between exposed and unexposed individuals. Ever-users of metformin were younger, more socially deprived, and had a higher proportion of men and higher Hb, BMI, and eGFR.

Study Period and Outcome

A total of 1,458 individuals (41.8%) had a moderate anemia event during the follow-up period: 745 in current users, 194 in former users, and 519 in never-users. The median (interquartile range [IQR]) follow-up time was 8.3 (5.0, 11.5) years, number of Hb measures per individual in the model was 11 (6, 20), and frequency of measures was 7.6 (4.5, 13.5) months.

Effects of Cumulative Metformin Exposure

Figure 2 shows the unadjusted rates of anemia by cumulative exposure to metformin standardized (within 10-year age bands) to the age distribution (over all person-years) of the whole study population. With increasing cumulative exposure, there is a higher risk of moderate anemia in metformin users, which is linear after an initial high rate in the 1st year. Because ever-users were younger with higher Hb at diagnosis (Table 1), it is unlikely that this group of individuals was at higher prior risk of anemia. It is more

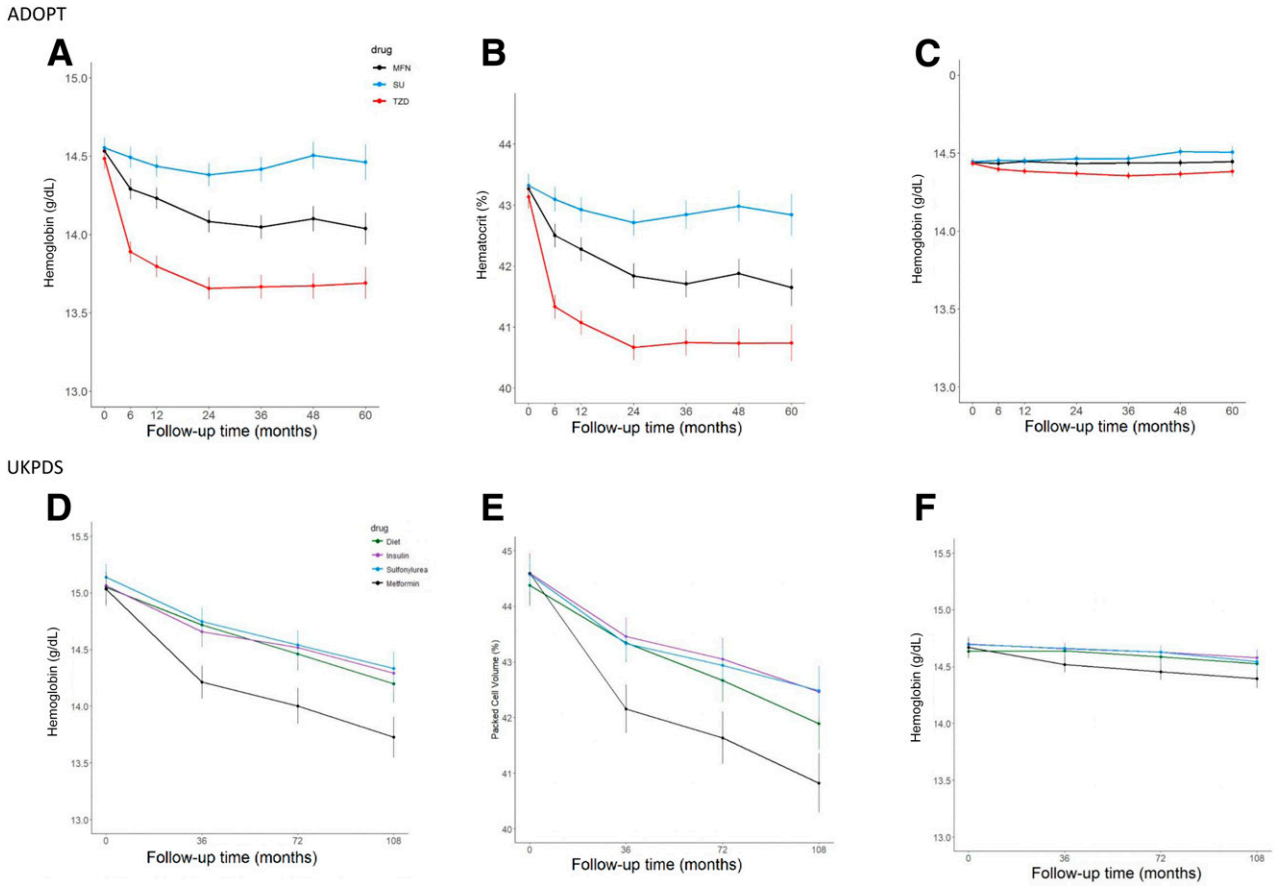

Figure 1—Plots of hematological changes over time using nonlinear mixed models. Data are presented as plots of predictions of the fixed effects for each treatment at each study visit. ADOPT trial: Hb (*A*), Hct (*B*), and Hb adjusted for Hct (*C*). UKPDS trial: Hb (*D*), PCV (*E*), and Hb adjusted for PCV (*F*).

likely that this initial greater risk of anemia with metformin can be attributed to an immediate effect of metformin on Hb, particularly in light of the ADOPT data where we see a significant change at 6 months (Fig. 1*A*).

Discrete-Time Failure Model

The results for the discrete-time failure analysis are presented in Table 2. In a simple model (model 1) with no diabetes drugs included, older age, longer duration of diabetes, lower baseline Hb, and higher social deprivation were associated with higher anemia risk. There was no difference by sex or calendar year of diagnosis, so these covariates were not included in subsequent models. In model 2a, cumulative exposure and ever-exposure to metformin were added. The OR (95% CI) per year of cumulative exposure to metformin was 1.05 (1.02, 1.08). In model 2b, cumulative metformin exposure is expressed as total dose (1.02 [1.01, 1.04] per 1 year of 1 g/day). The results of adjusting for all diabetes drug classes are presented in model 3, and the association of cumulative metformin with moderate anemia risk remains. In addition, there was an association between cumulative exposure to SGLT2i inhibitors and lower risk of moderate anemia (OR 0.46 [95% CI 0.36, 0.59]).

For a subgroup of patients where longitudinal measures of BMI ($n = 3,335$) and eGFR ($n = 2,920$) were available, these were added to the model as time-dependent covariates. BMI was not significantly associated with moderate anemia risk (data not shown). However, a lower eGFR was associated with a higher moderate anemia risk (model 4).

CONCLUSIONS

In this study we show for the first time that metformin use is associated with the risk of moderate anemia in individuals with type 2 diabetes and that this finding is consistent across two RCTs and replicated in one real-world study of routinely collected data. Furthermore, in the large, observational, population-based study with a maximum follow-up period of almost 20 years, we show that each 1 g/day of metformin use was associated with a 2% higher risk of moderate anemia per year.

Moderate Anemia Risk With Metformin Treatment in ADOPT and UKPDS

In the ADOPT study we observe the well-described early reduction in Hb seen with the initiation of TZD treatment, an effect seen premarketing and included in the summary of product characteristics (https://www.medicines.org.uk/emc/medicine/4236). We observe a similar pattern in the metformin-treated group in ADOPT, with an early fall in Hb, with no subsequent change after the first 2 years. These early changes in Hb (translated into moderate anemia events) are matched by findings, albeit observational as opposed to trials, in the real-world GoDARTS data. Similarly, in UKPDS, the main difference in Hb between the metformin and other treatment arms had occurred by the first measurement at 3 years. The finding in ADOPT, and to a

Table 1—Comparison of characteristics at diabetes diagnosis between never-users and eventual users of metformin

	Metformin user during the study		
	Never, $n = 998$	Ever, $n = 2,487$	P
Age (years)	68.3 (10.0)	60.5 (10.1)	<0.0001
% males	50	57.7	<0.0001
Year of diagnosis	2005.0 (4.5)	2003.4 (3.8)	<0.0001
Social deprivation			
1 (most deprived)	26.1	27.7	
2	20.5	22.2	
3	15.1	16.6	
4	19.4	16.9	
5	18.9	16.7	0.0301
Hb (g/dL)			
All	14.3 (1.2)	14.8 (1.2)	<0.0001
Males	15.0 (1.1)	15.3 (1.1)	<0.0001
Females	13.7 (1.0)	14.1 (1.0)	<0.0001
BMI (kg/m^2)	30.6 (5.7)	32.5 (6.1)	<0.0001
eGFR (mL/min per 1.73^2)	75.2 (20.4)	87.5 (18.3)	<0.0001

Data are presented as means (SD) or %. Comparisons are t test for continuous and χ^2 test for categorical variables.

large extent in UKPDS, that the fall in Hct (PCV) mirrors the fall in Hb is consistent with the anemia being caused by a reduction in red cell mass or an increase in plasma volume, or both. The fall in Hct (and Hb) seen with the TZDs is usually attributed to fluid retention and hemodilution, although other mechanisms have been proposed, such as a reduction in erythropoiesis due to a direct effect on the bone marrow or secondary to lowering insulin levels (13). For metformin, it is not possible to infer a mechanism for the early reduction in Hb we observed in the data we had access to. In UKPDS, we show no treatment-specific effect of metformin on plasma sodium, albumin, urea, white blood cell count, or AST (data not shown) that might collectively point to hemodilution, bone marrow suppression, or hemolysis. However, it seems unlikely that the mechanism for these early changes in Hb is secondary to B_{12} deficiency, because individuals should have enough B_{12} stored to last for between 2 and 5 years (3). Furthermore, the MCV during the 5-year ADOPT study did not increase with metformin treatment (Supplementary Fig. 1), and in the GoDARTS study, of those who developed anemia in the metformin-exposed group compared with the non-metformin-exposed group, microcytic anemia was more frequent (12.1% vs. 7.3%) and macrocytic less frequent (7.6% vs. 12.3%) (data not shown), suggesting that the anemia is not caused by a B_{12} deficiency.

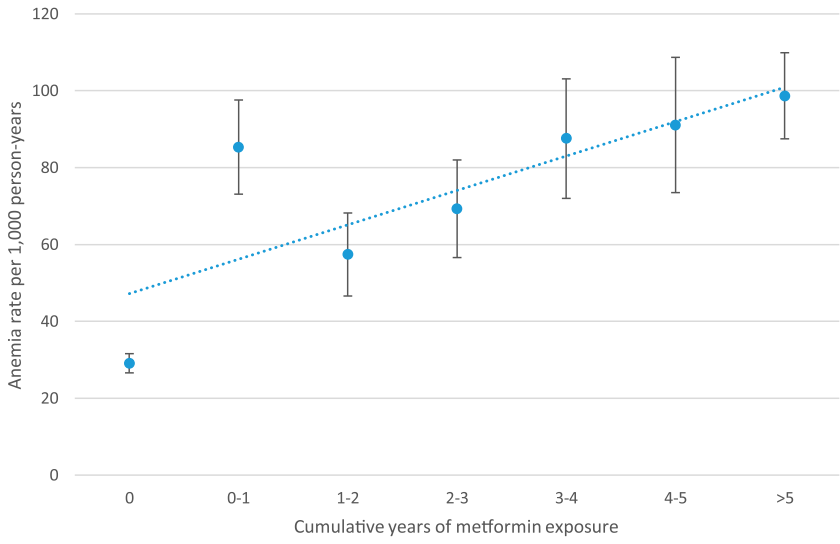

Figure 2—Plot of unadjusted rates of anemia by cumulative exposure to metformin standardized (within 10-year age bands) to the age distribution (overall person-years) of the whole study population. The terms for ever-exposure and cumulative exposure were given a visual representation by plotting a regression line through the unadjusted rates of anemia grouped by cumulative metformin exposure, representing the linear effect of cumulative exposure.

Predictors of Moderate Anemia Risk in GoDARTS

In the GoDARTS discrete-time failure model, we confirm the known predictors of anemia risk in type 2 diabetes, namely, older age, longer duration of diabetes, lower baseline Hb, and lower eGFR (measured time dependently), adding external validity to our model.

The association between cumulative SGLT2i exposure and an apparent "protective" effect on anemia risk is in line with RCT findings from the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study (14), which showed that Hct increases soon after the initiation of SGLT2i therapy and remains elevated for the duration of treatment. Elevation of Hct has generally been interpreted as indicating hemoconcentration due to the diuretic effect of SGLT2i.

It is perhaps surprising, given the ADOPT results, that cumulative exposure of TZD was not associated with anemia risk in GoDARTS. This is most likely an artifact of the model, given metformin is the first-line drug for most individuals and the study outcome is time to incident anemia; therefore, susceptible individuals are more likely to experience an event during their metformin exposure and drop out of the study before starting TZDs.

Overall Anemia Rates

The overall moderate anemia rates for the GoDARTS, ADOPT, and UKPDS studies were 41.8, 3.4 and 2.2%, respectively. The obvious reasons for the large difference between the real-world data and the trials are the GoDARTS population is older at diagnosis and monitored for longer, with a mean (SD) age at diagnosis 62.7 (10.6) vs. 52.8 (8.1) years in UKPDS and 56.6 (10.0) years in ADOPT, and a median

Table 2—Discrete-time failure models for moderate anemia in GoDARTS

	OR	95% CI	*P*
Model 1			
Age at diagnosis (per 1 year)	1.05	1.04, 1.05	**<0.0001**
Time from diagnosis (per 1 year)	1.11	1.09, 1.12	**<0.0001**
Calendar year of diagnosis (per 1 year)	0.99	0.98, 1.01	0.8405
Hb at diagnosis (per 1 g/dL)	0.71	0.67, 0.75	**<0.0001**
Females (vs. males)	1.05	0.94, 1.18	0.3841
Social deprivation (per one category [most deprived lowest])	0.96	0.93, 0.99	**0.0285**
Model 2a			
Age at diagnosis (per 1 year)	1.05	1.04, 1.06	**<0.0001**
Time from diagnosis (per 1 year)	1.08	1.06, 1.10	**<0.0001**
Hb at diagnosis (per 1 g/dL)	0.70	0.66, 0.73	**<0.0001**
Social deprivation (per one category [most deprived lowest])	0.96	0.93, 0.99	**0.0396**
Ever metformin	1.12	0.98, 1.28	0.1045
Cumulative metformin (per 1 year)	1.05	1.02, 1.08	**0.0002**
Model 2b			
Age at diagnosis (per 1 year)	1.05	1.04, 1.06	**<0.0001**
Time from diagnosis (per 1 year)	1.08	1.06, 1.10	**<0.0001**
Hb at diagnosis (per 1 g/dL)	0.69	0.66, 0.73	**<0.0001**
Social deprivation (per one category [most deprived lowest])	0.96	0.93, 0.99	**0.0366**
Ever metformin	1.16	1.02, 1.32	**0.0224**
Cumulative metformin dose (per 1 year of 1 g daily)	1.02	1.01, 1.04	**0.0001**
Model 3			
Age at diagnosis (per 1 year)	1.05	1.04, 1.06	**<0.0001**
Time from diagnosis (per 1 year)	1.07	1.05, 1.09	**<0.0001**
Hb at diagnosis (per 1 g/dL)	0.69	0.65, 0.73	**<0.0001**
Social deprivation (per one category [most deprived lowest])	0.96	0.93, 0.99	**0.0440**
Ever metformin	1.09	0.95, 1.25	0.2217
Ever sulfonylurea	1.04	0.90, 1.21	0.5668
Ever TZD	1.05	0.83, 1.32	0.6768
Ever insulin	1.43	1.12, 1.83	**0.0043**
Ever GLP-1 RA	0.51	0.25, 1.03	0.0588
Ever DPP4i	0.83	0.58, 1.18	0.2953
Ever SGLT2i	0.55	0.08, 3.96	0.5562
Ever glinide	0.89	0.40, 2.01	0.7825
Ever acarbose	0.82	0.37, 1.82	0.6225
Cumulative metformin (per 1 year)	1.06	1.03, 1.08	**<0.0001**
Cumulative sulfonylurea (per 1 year)	1.01	0.98, 1.04	0.5404
Cumulative TZD (per 1 year)	0.99	0.92, 1.07	0.9082
Cumulative insulin (per 1 year)	0.98	0.93, 1.04	0.5254
Cumulative GLP-1 RA (per 1 year)	1.10	0.85, 1.44	0.4689
Cumulative DPP4i (per 1 year)	0.95	0.77, 1.17	0.6307
Cumulative SGLT2i (per 1 year)	0.46	0.36, 0.59	**<0.0001**
Cumulative glinide (per 1 year)	1.02	0.70, 1.48	0.9307
Cumulative acarbose (per 1 year)	0.91	0.58, 1.42	0.6710
Model 4			
Age at diagnosis (per 1 year)	1.03	1.02, 1.04	**<0.0001**
Time from diagnosis (per 1 year)	1.05	1.03, 1.08	**<0.0001**
Hb at diagnosis (per 1 g/dL)	0.70	0.66, 0.74	**<0.0001**
Social deprivation (per one category [most deprived lowest])	0.97	0.93, 1.01	0.1906
eGFR (per 1 mL/min per 1.73^2)	0.98	0.98, 0.99	**<0.0001**
Ever metformin	1.16	0.99, 1.37	0.0760
Ever sulfonylurea	0.99	0.84, 1.18	0.9451
Ever TZD	1.04	0.80, 1.36	0.7593
Ever insulin	1.31	0.99, 1.72	0.0525
Ever GLP-1 RA	0.71	0.32, 1.57	0.3992
Ever DPP4i	1.00	0.67, 1.50	0.9947
Ever SGLT2i	0.96	0.13, 6.96	0.9644
Ever glinide	0.55	0.20, 1.50	0.2428
Ever acarbose	0.91	0.41, 2.03	0.8132
Cumulative metformin (per 1 year)	1.06	1.02, 1.09	**0.0006**
Cumulative sulfonylurea (per 1 year)	1.00	0.97, 1.04	0.8184
Cumulative TZD (per 1 year)	0.98	0.90, 1.07	0.6533

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study duration of 8.3 (IQR 5.0, 11.5) years compared with a maximum 5 years of follow-up in ADOPT and 9 years in UKPDS. In addition, Hb was measured more frequently in the GoDARTS population due to the observational nature of the study, where all routinely collected measures were included, resulting in a median number of 11 (IQR 6, 20) Hb measures per individual compared with a maximum of 4 in UKPDS and 7 in ADOPT, thus increasing the chances of a moderate anemia event being detected. In addition, those patients in ADOPT or UKPDS who develop anemia do not automatically drop out of the analysis and could be treated, thus potentially explaining the difference between the persisting risk of anemia with metformin in the observational GoDARTS study compared with in the ADOPT RCT. However, it is important to note that in the GoDARTS study, we only included 54% of the population, because a baseline Hb was required (characteristics of included and excluded individuals are provided in Supplementary Table 3) and these individuals would be expected to have been at a greater risk of anemia (by virtue of it being requested by health care professional), and so the overall rate may be an overestimate for the general population.

Limitations

The main limitation of the reported studies is the lack of B_{12} measurement and lack of other data to help point to a mechanism mediating the early reduction in Hb caused by metformin treatment. Careful studies assessing water balance and red cell production and turnover are warranted to better understand how metformin is causing a reduction in Hb.

A post hoc analysis of RCT data may be considered a limitation. However, in the absence of a specifically designed prospective study, there are very few RCTs of metformin. ADOPT and UKPDS are perhaps the best two trials of sufficient size and quality to address this question.

Conclusion

In this study, including data from two RCTs, albeit post hoc, we have shown that metformin consistently causes an early reduction in Hb and increases rates of moderate anemia. The absolute Hb reductions are not large (0.5 g/dL at 5 years with ADOPT, 0.5 g/dL at 3 years with UKPDS), although this does translate to a

Table 2—Continued

	OR	95% CI	*P*
Cumulative insulin (per 1 year)	0.99	0.93, 1.05	0.6753
Cumulative GLP-1 RA (per 1 year)	1.06	0.79, 1.43	0.6876
Cumulative DPP4i (per 1 year)	0.88	0.69, 1.11	0.2754
Cumulative SGLT2i (per 1 year)	0.40	0.26, 0.62	**<0.0001**
Cumulative glinide (per 1 year)	1.20	0.83, 1.72	0.3352
Cumulative acarbose (per 1 year)	0.86	0.54, 1.36	0.5102

Bold *P* values are statistically significant ($P < 0.05$).

large increase in moderate anemia rates, with an overall effect in the real-world population study of a 2% increased risk of anemia per year per 1 g/day of metformin (greater in the 1st year). Because the mechanisms for metformin-related moderate anemia are unknown, the effects are modest, and the benefits of metformin are proven, we would not in any way advocate avoidance or discontinuation of metformin, even in patients with anemia, but a reduction in Hb in the first few years after initiation of metformin might be anticipated.

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