Optimization of Metformin in the GRADE Cohort: Effect on Glycemia and Body Weight

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OBJECTIVE

We evaluated the effect of optimizing metformin dosing on glycemia and body weight in type 2 diabetes.

RESEARCH DESIGN AND METHODS

This was a prespecified analysis of 6,823 participants in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) taking metformin as the sole glucose-lowering drug who completed a 4- to 14-week (mean ± SD 7.9 ± 2.4) run-in in which metformin was adjusted to 2,000 mg/day or a maximally tolerated lower dose. Participants had type 2 diabetes for <10 years and an HbA_{1c} ≥6.8% (51 mmol/mol) while taking ≥500 mg of metformin/day. Participants also received diet and exercise counseling. The primary outcome was the change in HbA_{1c} during run-in.

RESULTS

Adjusted for duration of run-in, the mean ± SD change in HbA_{1c} was −0.65 ± 0.02% (−7.1 ± 0.2 mmol/mol) when the dose was increased by ≥1,000 mg/day, −0.48 ± 0.02% (−5.2 ± 0.2 mmol/mol) when the dose was unchanged, and −0.23 ± 0.07% (−2.5 ± 0.8 mmol/mol) when the dose was decreased (n = 2,169, 3,548, and 192, respectively). Higher HbA_{1c} at entry predicted greater reduction in HbA_{1c} (P < 0.001) in univariate and multivariate analyses. Weight loss adjusted for duration of run-in averaged 0.91 ± 0.05 kg in participants who increased metformin by ≥1,000 mg/day (n = 1,894).

CONCLUSIONS

Optimizing metformin to 2,000 mg/day or a maximally tolerated lower dose combined with emphasis on medication adherence and lifestyle can improve glycemia in type 2 diabetes and HbA_{1c} values ≥6.8% (51 mmol/mol). These findings may help guide efforts to optimize metformin therapy among persons with type 2 diabetes and suboptimal glycemic control.

Metformin is widely recommended as first-line therapy for management of hyperglycemia in patients with type 2 diabetes (1). Metformin is inexpensive, rarely associated with hypoglycemia when used alone, has beneficial effects on body weight and lipids, and appears to reduce the risk of cardiovascular events (2). Most individuals tolerate metformin well, although gastrointestinal side effects may require a switch to long-acting formulations, dose reduction, or discontinuation. While vitamin B12 deficiency can complicate therapy (3), lactic acidosis appears to be extremely rare when the drug is used appropriately (4).

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Metformin is approved up to a total daily dose of 2,550 mg (or 2,000 mg/day for the extended-release [XR] form), although 2,000 mg/day is often considered the optimal dose, because higher doses may be associated with increased gastrointestinal side effects with marginal glycemic benefit (5). When administered as monotherapy to participants not receiving any other antidiabetic drug, metformin can reduce HbA_{1c} by up to 2.0% (6,7) depending on baseline HbA_{1c} levels and dose. However, the incremental effect of metformin when the dose is increased in persons taking less than a maximum dose is not clear. This is a relevant clinical issue, particularly for patients taking <2,000 mg/day who may have HbA_{1c} values within a designated target range but still above normal and, hence, have suboptimal glycemic control. Metformin, when used alone, rarely causes hypoglycemia and is generally safe even in patients who do not have diabetes (8,9). Therefore, in most cases, there is little downside to increasing the dose to improve diabetes control. However, to improve our understanding of this issue, it would help to better define the extent to which average glycemia can be improved by optimizing metformin dosing.

The ongoing Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) offers insight in this respect. GRADE is designed to determine the relative effectiveness of four commonly used glucose-lowering medications when added to metformin. A run-in phase was conducted prior to randomization. To enter run-in, participants had to be taking metformin as the sole glucose-lowering medication and to have HbA_{1c} levels ≥6.8% (51 mmol/mol). Although a large portion of participants entered run-in on a prescribed dosage of 2,000 mg/day, the actual dosage varied. During run-in, the dose was either maintained at 2,000 mg/day or adjusted, as tolerated, toward a goal of 2,000 mg/day. The dose adjustments included attempts to increase the dose to 2,000 mg/day in participants on less than that amount and to decrease the dose to 2,000 mg/day in participants taking more than that amount. In this study, we report the impact of optimizing metformin dose during the run-in phase of the GRADE study on glycemic control and body weight and evaluate predictors of glycemic response.

RESEARCH DESIGN AND METHODS

Study Design

GRADE is a multicenter randomized trial designed to assess the comparative effectiveness of glargine insulin, glimepiride, sitagliptin, and liraglutide when added to metformin. The GRADE protocol was described in detail in 2013 (10). A total of 11,230 volunteers underwent screening, including measurement of HbA_{1c}; 7,764 participants returned for an initial run-in visit. Of those who had an initial run-in visit and a screening HbA_{1c}, 6,850 (88.2%) completed the run-in. Recruitment for GRADE began in May 2013 and concluded in July 2017.

Eligibility

To be eligible for run-in, participants had to have had type 2 diabetes for ≤10 years and HbA_{1c} ≥6.8% (51 mmol/mol) while taking ≥500 mg of metformin daily for at least 8 weeks prior to starting the run-in. To be eligible for randomization, participants had to complete a run-in period of 6–14 weeks if they were taking metformin at a dose other than 2,000 mg/day prior to screening or at least 4 weeks if taking 2,000 mg/day at the time of screening. For participants taking metformin 2,000 mg daily at screening, the daily dose was maintained at that level unless it had to be reduced due to intolerance. For participants taking a dose <2,000 mg/day or >2,000 mg/day, the dose was adjusted to 2,000 mg/day as tolerated. Participants were advised to take metformin with meals. Some participants who could not tolerate 2,000 mg/day of the immediate-release (IR) formulation were switched to the XR formulation to facilitate titration to 2,000 mg/day.

A total of 914 participants entered but did not complete run-in. A total of 300 reasons could be ascertained in 252 participants; 63 no longer met eligibility criteria, 83 were not judged an acceptable candidate, and 154 declined further participation (16 cited lack of time, 24 cited conflicting responsibilities, 24 cited concern about being assigned to an injectable medication, and 23 cited side effects from metformin).

Study Outcomes

The primary outcome was the change in HbA_{1c} between the screening and final run-in visits. HbA_{1c} was measured in blood samples obtained at the screening visit or within 30 days of that visit. Screening HbA_{1c} measurements were performed at local clinical laboratories. HbA_{1c} at final run-in was determined on samples sent to the study core laboratory at the University of Minnesota. Secondary outcome was change in weight, measured twice in light clothing, with the average used. Body weight was determined at the screening visit and again at either the final run-in or randomization visit. Adherence was determined based on participants' self-reported responses to a questionnaire administered at the final run-in visit.

Data Analysis and Statistics

This study was performed as a prespecified analysis based on a proposal written before any analysis was done and reviewed and approved by the GRADE Study Publications and Presentations Subcommittee. This report was restricted to the run-in phase (mean ± SD duration of 7.9 ± 2.4 weeks).

Data are expressed as means and SDs for quantitative variables and counts and column percentages for qualitative variables. Comparisons between males and females were performed using the χ^2 test of independence for qualitative variables and the Student *t* test with unequal variances for quantitative variables. The means and CIs in Fig. 1*A* and *B* are least-squares means and their 95% CIs from least squares regression models, which included duration of run-in as a covariate to adjust for nonuniform run-in periods. Supplementary Figure 1 plots change in HbA_{1c} against screening HbA_{1c}, and regression lines were estimated over the range from 6.8% (51 mmol/mol) to 8.0% (64 mmol/mol) by fitting an ANCOVA model for change in HbA_{1c} as a function of screening HbA_{1c}, an indicator for metformin change <1,000 mg/day, and an interaction between screening HbA_{1c} and the indicator. The *P* value for the interaction term in this model was used to test equality of slopes. Dropping the interaction term in this model and obtaining the *P* value for the indicator for metformin <1,000 mg/day provided a test for a difference in intercepts. The trend lines in Supplementary Fig. 2 are from locally weighted scatterplot smoothers. Data were analyzed using R version 3.5.1.

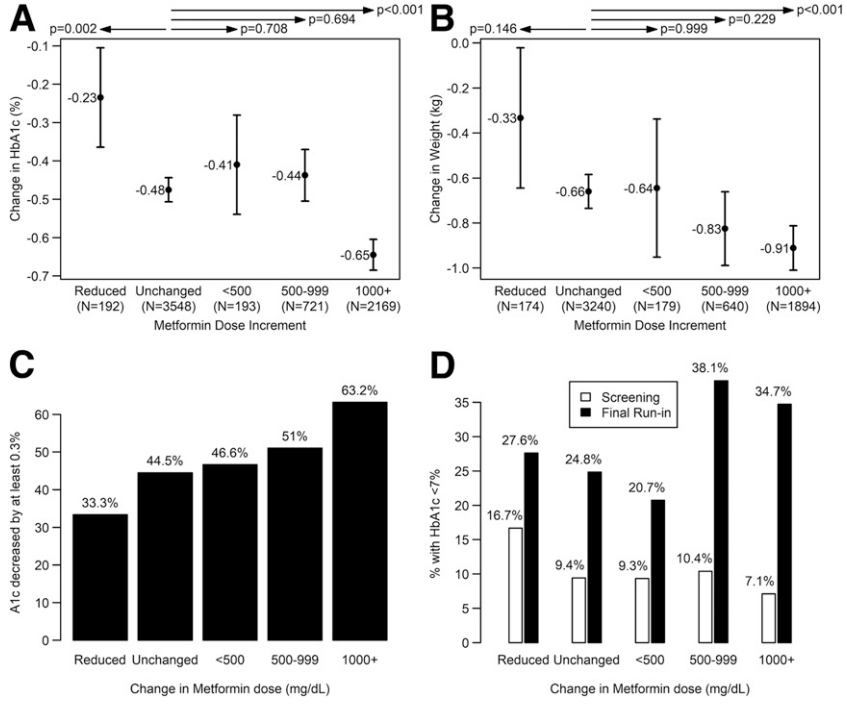

Figure 1—Dose-dependent effects of metformin on glycemia and body weight. Changes with 95% CIs in HbA_{1c} (*A*) and body weight (*B*) by magnitude of metformin dose change during run-in. Numerical mean values are listed within the bars. Actual mean ± SD dose changes for reduced, unchanged, and <500, 500–999, and ≥1,000 mg/day, respectively, were −602 ± 245, 0 ± 0, 295 ± 22, 503 ± 28, and 1,084 ± 183 in *A* and −608 ± 250, 0 ± 0, 296 ± 20, 504 ± 29, and 1,080 ± 180 in *B*. *C*: Bars representing binary variable based on whether HbA_{1c} (A1c) had improved by 0.3% (3.3 mmol/mol) or better (−0.3% is the median change); $P < 0.001$ by χ^2 test. *D*: Proportion of participants with an HbA_{1c} <7% (53 mmol/mol) before and after the run-in. The data in *A* and *B* are based on a regression model with HbA_{1c} change or weight change as the response and the category of metformin change as a predictor, adjusted for duration of run-in. The estimates and error bars are from the least squares means for metformin change and their 95% CIs. The *P* values are calculated from contrasts between the least squares means and are adjusted for multiple comparisons using a Dunnett adjustment. HbA_{1c} values in percentage units can be converted to millimoles per mole using the NGSP HbA_{1c} converter at https://www.ngsp.org/convert1.asp.

RESULTS

Participant Characteristics (Baseline and Final Run-in)

A total of 6,823 participants completed the run-in and had reported metformin doses and HbA_{1c} measurements at screening and at a final run-in visit. This included 5,039 out of 5,047 randomized GRADE participants, as 8 of the 5,047 were missing HbA_{1c} values at screening and could not be included in the analyses. This also included 1,784 who completed run-in but were not randomized because of ineligibility due to a final screening A1C outside the range of 6.8–8.5% (51–69 mmol/mol) inclusive (83% of the 1,784) or because they decided not to take a second drug, not to accept injections, or not to comply with other study requirements. Baseline characteristics determined at the initial run-in visit as well as changes in HbA_{1c}, weight, metformin dosing, and metformin adherence during run-in are reported by sex in Table 1. Weight change could be calculated on 6,127 out of the 6,823 participants with complete HbA_{1c} and metformin information. The predominance of male participants reflects participants recruited at Veterans Health Administration sites at which the male patient population is substantially higher. There was no sex difference in initial (screening) HbA_{1c}.

Metformin Formulation and Adherence

Adherence data (Table 1) showed that 77.1% of all participants reported never missing a medication dose in the past week, while 1.8% of the participants reported missing ≥20% of the doses. Male participants reported slightly better adherence than females. At the initial run-in, 73.5% of the participants were on immediate-acting metformin IR, and 26.5% were on long-acting metformin XR. During run-in, 8.0% of participants initially on metformin IR and 2.9% of participants on XR switched metformin type. At completion of run-in, the proportions on IR and XR were 68.4% and 31.6%, respectively. There were no reports of severe hypoglycemia (requiring assistance from a third party) or gastrointestinal effects judged as severe adverse events during run-in.

Effect of Changes in Metformin Dosing on Glycemic Control and Body Weight

HbA_{1c} levels, adjusted for duration of run-in (Fig. 1) or unadjusted (Table 2), decreased dependent on the magnitude of change in metformin dose. As shown in Fig. 1*A*, this included a decline in HbA_{1c} even in participants whose dose of metformin did not change (−0.48 ± 0.02% [−5.2 ± 0.2 mmol/mol]). Therefore, in assessing the effect of metformin dose changes on glycemic control (Fig. 1*A*), the group that did not change metformin dose was used as an internal control in the sense that tests of contrasts were done comparing the metformin dose change groups with the internal control group (adjusting for duration of run-in). The decrease in HbA_{1c} was significantly greater than this internal control group only for participants who increased the metformin dose by ≥1,000 mg/day (−0.65 ± 0.02% [−7.1 ± 0.2 mmol/mol]; $P < 0.001$). Of additional note, participants who reduced their metformin dose had a significantly smaller drop in HbA_{1c} than the internal control group that did not reduce the metformin dose (−0.23 ± 0.07% [−2.5 ± 0.8 mmol/mol]; $P = 0.002$). Similar to changes in HbA_{1c}, there was a decrease in weight in participants whose dose of metformin did not change (−0.66 ± 0.04 kg) (Fig. 1*B*). We again used the group that did not change metformin dose as an internal control (adjusting for duration of run-in). Weight decreased significantly compared with the internal control group only in participants who increased their metformin dose by ≥1,000 mg/day (−0.91 ± 0.05 kg; $P < 0.001$), while weight loss was nonsignificantly lower in participants whose metformin dose was reduced (−0.33 ± 0.16 kg; $P = 0.146$).

Among the participants in the no-change control group, 199 entered run-in taking <2,000 mg metformin/day. Therefore,

Table 1—Characteristics by sex of GRADE participants at initial run-in and findings at the final run-in visit

	All	Female	Male	*P* value
Characteristics at initial run-in visit				
N	6,823	2,519	4,304	
Age (years)*	56.1 ± 10.1	54.5 ± 9.7	57.1 ± 10.2	<0.001
Duration of run-in (weeks)	7.9 ± 2.4	8.1 ± 2.5	7.8 ± 2.3	<0.001
Race				<0.001
Caucasian	4,319 (63.3)	1,350 (53.6)	2,969 (69.0)	
Native American	193 (2.8)	112 (4.4)	81 (1.9)	
Asian	240 (3.5)	61 (2.4)	179 (4.2)	
Hawaiian/Pacific Islander	47 (0.7)	9 (0.4)	38 (0.9)	
African American	1,478 (21.7)	747 (29.7)	731 (17.0)	
Other/multiple	450 (6.6)	200 (7.9)	250 (5.8)	
Unknown/not reported	96 (1.4)	40 (1.6)	56 (1.3)	
Hispanic	1,302 (19.2)	601 (24.1)	701 (16.4)	<0.001
Weight (kg)	100.3 ± 22.5	93.4 ± 21.7	104.4 ± 21.9	<0.001
Height (cm)	170.3 ± 10.0	161.6 ± 7.1	175.5 ± 7.5	<0.001
BMI (kg/m^2)	34.5 ± 6.8	35.6 ± 7.4	33.9 ± 6.3	<0.001
Creatinine (mg/dL)	0.82 ± 0.20	0.69 ± 0.16	0.90 ± 0.18	<0.001
Lipids (mg/dL)*				
Total cholesterol	163.8 ± 37.8	172.7 ± 37.1	158.7 ± 37.2	<0.001
HDL	43.3 ± 12.1	48.2 ± 13.0	40.5 ± 10.6	<0.001
LDL	90.7 ± 31.5	96.4 ± 32.0	87.3 ± 30.7	<0.001
Triglycerides	125.0 (88.0, 184.0)	122.0 (86.0, 175.0)	128.0 (89.0, 190.0)	<0.001
HbA_{1c} (%) at screening visit	8.1 ± 1.2	8.1 ± 1.2	8.1 ± 1.2	0.509
Metformin dose (mg/day) at screening visit				<0.001
<1,000	516 (7.6)	204 (8.1)	312 (7.2)	
1,000–1,499	2,115 (31.0)	861 (34.2)	1,254 (29.1)	
1,500–1,999	672 (9.8)	229 (9.1)	443 (10.3)	
2,000	3,424 (50.2)	1,201 (47.7)	2,223 (51.6)	
≥2,000	96 (1.4)	24 (1.0)	72 (1.7)	
Findings at final run-in visit				
HbA_{1c} (%)				
Final run-in visit	7.6 ± 0.9	7.6 ± 0.9	7.6 ± 0.9	0.523
Change	−0.52 ± 0.94	−0.51 ± 0.91	−0.52 ± 0.95	0.822
Weight change (kg) during run-in	−0.74 ± 2.10	−0.70 ± 1.95	−0.77 ± 2.19	0.185
Metformin dose (mg/day)				
Final run-in visit				<0.001
<1,000	2 (0.0)	0 (0.0%)	2 (0.0)	
1,000–1,499	284 (4.2)	133 (5.3%)	151 (3.5)	
1,500–1,999	348 (5.1)	188 (7.5%)	160 (3.7)	
2,000	6,189 (90.7)	2,198 (87.3%)	3,991 (92.7)	
Change				<0.001
Reduced	192 (2.8)	70 (2.8)	122 (2.8)	
Unchanged	3,548 (52.0)	1,250 (49.6)	2,298 (53.4)	
<500	193 (2.8)	53 (2.1)	140 (3.3)	
500–999	721 (10.6)	321 (12.7)	400 (9.3)	
≥1,000	2,169 (31.8)	825 (32.8)	1,344 (31.2)	
Metformin type at final run-in				<0.001
IR	4,665 (68.4)	1,596 (63.4)	3,069 (71.3)	
XR	2,158 (31.6)	923 (36.6)	1,235 (28.7)	
Percent of pills missed last week				<0.001
0	4,852 (71.1)	1,725 (68.5)	3,127 (72.7)	
0–20	1,848 (27.1)	749 (29.7)	1,099 (25.5)	
>20	120 (1.8)	44 (1.7)	76 (1.8)	

Continuous variables are shown as the mean ± SD with a *P* value comparing males to females based on a two-sample *t* test with unequal variances. As an exception, triglycerides are shown as median (interquartile range) and analyzed by nonparametric rank test due to skew in the data. For categorical values, the table shows the number of participants and percentages for each category and a χ^2 *P* value comparing males to females. HbA_{1c} values in percentage units can be converted to millimoles per mole using the NGSP HbA_{1c} converter at https://www.ngsp.org/convert1.asp. *Age is indicated as reported at screening. Lipid measurements were carried out only at randomization, so HDL, LDL, and triglyceride values exclude 1,784 of the 6,823 participants who completed run-in but were not randomized.

we further analyzed the changes in HbA_{1c} and weight, excluding those participants (Supplementary Fig. 3). The results were similar (compare Fig. 1 and Supplementary Fig. 3) with no changes in statistical significance.

Because 914 participants entered but did not complete run-in, the data in Fig. 1*A* and *B* were reanalyzed in a sensitivity analysis incorporating all participants entering run-in by estimating inverse probability weights based on the propensity

Table 2—Participant data by magnitude of metformin dose change

	Metformin dose change					
	Reduced	Unchanged	<500	500–999	≥1,000	*P* value
N	192	3,548	193	721	2,169	
Duration of run-in (weeks)	7.2 ± 2.4	7.0 ± 2.3	8.5 ± 1.9	8.7 ± 1.9	9.1 ± 2.0	<0.001
HbA_{1c} (%)						
Screening visit	7.8 ± 0.9	8.1 ± 1.2	8.1 ± 1.3	7.9 ± 1.1	8.2 ± 1.3	<0.001
Final run-in visit	7.6 ± 0.9	7.6 ± 0.9	7.7 ± 0.9	7.4 ± 0.9	7.5 ± 1.0	<0.001
Change	−0.19 ± 0.67	−0.42 ± 0.90	−0.45 ± 1.05	−0.50 ± 0.87	−0.72 ± 0.99	<0.001
Metformin dosing (mg/day)						
Screening visit	2,219.3 ± 366.2	1,948.3 ± 217.1	1,668.4 ± 170.8	1,257.4 ± 326.5	904.9 ± 192.9	<0.001
Final run-in visit	1,617.2 ± 419.5	1,948.3 ± 217.1	1,963.7 ± 187.4	1,760.7 ± 325.9	1,988.7 ± 74.3	<0.001
Metformin type at final run-in						<0.001
IR	116 (60.4)	2,616 (73.7)	148 (76.7)	409 (56.7)	1,376 (63.4)	
XR	76 (39.6)	932 (26.3)	45 (23.3)	312 (43.3)	793 (36.6)	
Adherence to metformin						
Percentage of pills missed last week						<0.001
0	144 (75.0)	2,610 (73.6)	148 (76.7)	487 (67.5)	1,463 (67.5)	
0–20	43 (22.4)	891 (25.1)	43 (22.3)	209 (29.0)	662 (30.5)	
>20	5 (2.6)	44 (1.2)	2 (1.0)	25 (3.5)	44 (2.0)	

Continuous variables are shown as the mean ± SD with a *P* value based on an overall *F* test from an ANOVA. For categorical variables, the table shows the number of participants and percentages for each category and a χ^2 *P* value comparing the metformin dose-change categories. HbA_{1c} values in percentage units can be converted to millimoles per mole using the NGSP HbA_{1c} converter at https://www.ngsp.org/convert1.asp.

to finish run-in and repeating the analysis, applying these weights to the analytic sample of 6,823 participants who did complete run-in. This analysis revealed similar findings with no change in significance (data not shown). A further sensitivity analysis was performed on the data in Fig. 1*A* and *B*, stratified by whether participants received metformin IR or XR. Trends for the associations of metformin dose change with change in HbA_{1c} and change in weight were similar for those who received both IR and XR metformin. However, one exception was that those who received metformin XR and increased their dose <500 mg/day experienced a considerably smaller decrease in both HbA_{1c} and weight, although estimates for this subgroup were imprecise due to a small ($n = 45$ for HbA_{1c} and $n = 40$ for weight) subgroup size (data not shown).

Because of the large variability in change in HbA_{1c}, a binary variable was created based on whether HbA_{1c} had improved by 0.3% (3.3 mmol/mol) or better (−0.3% was the median change). There was a significant difference in the percent of participants achieving an HbA_{1c} decrease of at least 0.3% among metformin dose-change groups ($P < 0.001$ by χ^2) (Fig. 1*C*). There were also metformin dose-dependent differences in the percentage of participants reaching an HbA_{1c} <7.0% (53 mmol/mol) (Fig. 1*D*).

Parameters Predicting HbA_{1c} Change With Incremental Metformin

Regression analyses were carried out for several parameters expected to affect the change in HbA_{1c} following increments in metformin dosage (Table 3 and Supplementary Fig. 2). The dominant factor in multivariate analyses was the HbA_{1c} level prior to dose change. These relationships are depicted using nonlinear correlation for participants whose metformin dose was increased by ≥1,000 mg/day or changed by <1,000 mg/day (Supplementary Fig. 1). An inflection point is apparent just above an HbA_{1c} value of 8.0% (64 mmol/mol), suggesting a steeper relationship above that point. Linear regression was carried out in order to look at the change in HbA_{1c} as related to screening HbA_{1c} values between 6.8% and 8.0% (51 and 64 mmol/mol) in Supplementary Fig. 1. These values are in the range of often-cited target levels (11–13). Although the slopes did not differ, the differences in elevation of the curves indicated greater HbA_{1c}-lowering effect for dose increments ≥1,000 mg/day.

In addition to initial HbA_{1c} level, other factors associated with change in HbA_{1c} were examined in a multivariable model (Table 3). Factors significantly associated with a decrease in HbA_{1c} included older age; African American, Native American, or other/multiple race (compared with white race); Hispanic ethnicity; and higher creatinine. Factors significantly associated with an increase in HbA_{1c} included higher baseline weight and longer duration of diabetes.

CONCLUSIONS

We report the effect of adjusting metformin dosage in 6,823 participants with an initial HbA_{1c} level of ≥6.8% (51 mmol/mol) over a mean run-in period of 7.9 ± 2.4 weeks. Adjusting dosage to 2,000 mg/day or to a maximally tolerated lower dose was associated with a mean decrease in HbA_{1c} of 0.52 ± 0.94% (5.7 ± 10.3 mmol/mol). Greater increases in dosing were associated with greater reductions in HbA_{1c}. However, participants with no change in metformin dosing, and even those with a dose reduction, also exhibited decreases in HbA_{1c} levels, suggesting that improvement in adherence to the medication and/or lifestyle behavior also contributed.

Several reports have compared the effects of different doses of metformin on HbA_{1c} levels (5,7,14–19). For total daily doses of 1,000 mg versus 2,000 mg (15,16,19) or 1,500 mg versus 3,000 mg (17), improvements in HbA_{1c} were in the range of 0.2–0.3% (2.2–3.3 mmol/mol). However, another study (5) reported a difference of ~0.8% (8.7 mmol/mol) for 1,000 versus 2,000 mg daily after subtracting out the change in HbA_{1c} in placebo-treated participants. In that

Table 3—Factors associated with change in HbA_{1c} by univariate and multivariate analyses

Predictor	HbA_{1c} (%) change estimate	*P* value (univariate)	HbA_{1c} (%) change estimate	*P* value (multivariate)
HbA_{1c} (%) at screening	−0.4981	<0.001	−0.5003	<0.001
Age	0.0108	<0.001	−0.0052	<0.001
Race				
American Indian/Alaska Native	−0.854	<0.001	−0.4019	<0.001
Asian	0.0352	0.566	−0.0583	0.230
Hawaiian/Pacific Islander	−0.0241	0.859	0.0641	0.533
Black or African American	−0.1324	<0.001	−0.0915	<0.001
Other/multiple	−0.2919	<0.001	−0.0915	0.012
Unknown/not reported	−0.2769	0.004	−0.1966	0.010
Male	−0.0052	0.824	0.0289	0.184
Weight at screening	0.0026	<0.001	0.0022	<0.001
Hispanic	−0.2811	<0.001	−0.0816	0.001
Creatinine	0.2728	<0.001	−0.3141	<0.001
Diabetes duration	0.0405	<0.001	0.0444	<0.001

The coefficient estimates and *P* values are from least squares regression models. HbA_{1c} values in percentage units can be converted to millimoles per mole using the NGSP HbA_{1c} converter at https://www.ngsp.org/convert1.asp.

study, the placebo group had a 1.2% (13.1 mmol/mol) increase in HbA_{1c} over 14 weeks, while baseline HbA_{1c} values for all groups were relatively high at ~10.0% (86 mmol/mol).

Our current study differs from the above reports in an important way. Those studies compared the effectiveness of metformin in participants not previously taking the drug who were randomly assigned to different doses. In this study, we adjusted metformin dosing in persons already taking the drug, typical of what would be done in clinical practice. In some of the previous studies (14,18), comparative doses of metformin were examined in persons also taking another glucose-lowering drug. We are not aware of other studies that compared the effects of differential adjustments in metformin dosage in participants already taking the drug and not using another glucose-lowering drug.

Three smaller studies compared increments in metformin dosing from 1,000 to 2,000 mg/day to continuation of metformin 1,000 mg/day with additions of sitagliptin (20), vildagliptin (21), or rosiglitazone (22). Respectively, for participants whose metformin dose was increased, these studies showed changes in HbA_{1c} of −0.80% (−8.7 mmol/mol) from a baseline mean of 8.7% (72 mmol/mol), −0.37% (−4.0 mmol/mol) from a baseline mean of 7.3% (56 mmol/mol), and −0.71% (−7.8 mmol/mol) from a baseline mean of 8.0% (64 mmol/mol). These reports did not examine differential increments in metformin dosing and, importantly, did not provide a control group (metformin unchanged) to estimate the effect of lifestyle and adherence recommendations or of trial entry. Moreover, the relationships of increments in HbA_{1c} to pretreatment HbA_{1c} or other factors affecting metformin responsiveness were not assessed, beyond one report showing a greater effect of incrementing metformin in participants whose baseline HbA_{1c} was >8% (64 mmol/mol) compared with <8% (change of −0.46% or −5.0 mmol/mol vs. −0.31% or −3.4 mmol/mol). Taken together, the data from these studies are roughly in agreement with our findings.

We acknowledge that we adjusted metformin dosing in the context of a clinical trial in which the drug was provided free of cost and with emphasis on medication adherence, diet, and exercise. These factors may in part explain why participants with no change in metformin dose had a decrease in HbA_{1c} and weight. Moreover, there is evidence that glycemia improves upon entry into a clinical trial per se (23). Despite this, adherence and lifestyle modification alone cannot explain all of the improvement in HbA_{1c} with optimization of dosage, because HbA_{1c} fell significantly more in participants whose dose was increased by 1,000 mg/day, when compared with the group for which dose was unchanged (Fig. 1).

We observed that in participants whose metformin dose was reduced, either because they were taking >2,000 mg at the time of initial run-in or because of intolerance, HbA_{1c} improved less than in participants whose dose was unchanged (Fig. 1). The reduction in metformin dose was from an average of 2,219 to 1,617 mg/day, while the average metformin dose of those who were unchanged was 1,948 mg/day. This differs from an older report in which there was no difference in HbA_{1c} levels, with 2,500 mg daily compared with 2,000 mg/day (5). However, that study compared different doses in different individuals, whereas we made dose adjustments within the same participants. This discrepancy cannot be attributed to the emphasis on medication adherence and lifestyle change in our study, as that should not have differed among participants.

Although multiple factors beyond metformin dose change per se were predictive of the effect of metformin on HbA_{1c} levels, by far the strongest was the HbA_{1c} level prior to metformin dose adjustment (Table 3 and Supplementary Fig. 2). Baseline HbA_{1c} levels contributed independently both among participants whose dose was increased by ≥1,000 mg/day and for participants whose dose was not increased or increased by lesser amounts. In multivariate analyses, older age, African American, Native American, or other/multiple race (compared with white), Hispanic ethnicity, and higher creatinine levels were less strongly associated with a decrease in HbA_{1c} (Table 3), while higher weight and longer diabetes duration were associated with a mild increase. Consistent with our

findings, an examination of electronic health records of 19,672 patients showed that African American heritage was associated with a greater reduction in HbA_{1c} than European American following prescription of metformin (24). However, an association with race/ethnicity was not reported in other studies (25,26).

Adherence to metformin therapy during run-in appeared to be strong in that 71.1% of participants reported no missed pills in the past week, and 27.1% reported missing only 0–20% (Table 1). Further supporting tolerance to metformin, 90.7% of participants were at 2,000 mg/day (Table 1), and the mean dose at final screening was 1,932 mg/day. Importantly, intolerance was expected to be low, because all participants were required to be taking metformin in order to be eligible for screening. This may explain why nonadherence was lower in this study than in other reports (27).

The American College of Physicians (ACP) recently suggested a target HbA_{1c} value of 8.0% (64 mmol/mol) as appropriate for "most patients with type 2 diabetes" (12). Although many consider this ACP target of 8.0% as too high for many individuals (13), we point out that the curvilinear relationships in Supplementary Fig. 1 show that the impact of metformin dose adjustment was greater for those with an initial HbA_{1c} level of $\geq$8.0% (64 mmol/mol). Therefore, increasing metformin may be particularly effective for those with an HbA_{1c} level above the ACP target.

Our findings have broad clinical implications. Figure 1 shows that there is potential for metformin dose adjustment to improve glycemic control even in individuals with lower HbA_{1c} values or values already within guidelines (11–13). Moreover, Table 2 shows that participants whose dose was increased by $\geq$1,000 mg/day entered screening taking a mean of 905 mg metformin daily with a mean HbA_{1c} of 8.2% (66 mmol/mol). These observations, in common, suggest that there may be benefit from metformin dose adjustment in many patients with type 2 diabetes. In support of this concept, there were no reports of severe hypoglycemia during the GRADE run-in. Moreover, although not specifically tabulated, participant-reported hypoglycemia of any degree was very unusual, as expected based on other reports indicating that metformin causes little hypoglycemia, when used as the sole glucose-lowering drug (28–30). Further, we point out that metformin is often used in the absence of diabetes for prevention of the disease (8) or for therapy of polycystic ovarian disease in persons without diabetes (31).

In contrast, beyond hypoglycemia, there are other well-known adverse effects of metformin (4), and benefit must be considered relative to risk. We found that the fall in HbA_{1c} was very modest for individuals entering run-in with HbA_{1c} values in the lower range (Supplementary Fig. 1).

There are some limitations to this study. The run-in period was variable and as low as 4 weeks for participants entering the study already taking 2,000 mg/day, in whom the metformin dose was not changed. Thus, changes in HbA_{1c} in those with short duration of follow-up may have underestimated the effect that might have been seen if a usual interval HbA_{1c} had been obtained (i.e., $\geq$2 months). However, this effect may have been mitigated in that all participants had to be taking metformin for at least 8 weeks at the time of screening. As noted, we adjusted metformin dosing in the context of a clinical trial and, as per study protocol, this was done along with recommendations for medication adherence and changes in behavior, diet, and exercise. The initial HbA_{1c} values were determined by local laboratories, while the HbA_{1c} values at final run-in were all determined by our study core laboratory. However, the methodology for HbA_{1c} is now well standardized in relation to average glycemia and would not be expected to differ by baseline HbA_{1c} or metformin dose (32,33). Adherence to therapy was based on participant self-report rather than pill counts. Moreover, adherence to therapy should not have been affected by affordability, because metformin was provided free of cost to all participants.

In conclusion, adjusting metformin dosing to 2,000 mg/day or to a maximally tolerated lower dose combined with promoting lifestyle changes and medication adherence improved glycemic control by an average of 0.52% (5.7 mmol/mol) in patients who had an average HbA_{1c} of $\geq$6.8% (51 mmol/mol) and reported taking an average of 1,543 mg/day at baseline. The improvement was greater in those with a higher initial HbA_{1c}. These findings serve as a guide that could help to improve management in persons on submaximal metformin therapy.

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References

1. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl. 1):S73–S85
2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
3. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the diabetes prevention program outcomes study. J Clin Endocrinol Metab 2016;101:1754–1761
4. Bailey CJ. Metformin: historical overview. Diabetologia 2017;60:1566–1576
5. Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. Am J Med 1997;103:491–497
6. Nathan DM, Buse JB, Davidson MB, et al.; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193–203
7. Hirst JA, Farmer AJ, Ali R, Roberts NW, Stevens RJ. Quantifying the effect of metformin treatment and dose on glycemic control. Diabetes Care 2012;35:446–454
8. Hostalek U, Gwilt M, Hildemann S. Therapeutic use of metformin in prediabetes and diabetes prevention. Drugs 2015;75:1071–1094
9. Radosh L. Drug treatments for polycystic ovary syndrome. Am Fam Physician 2009;79:671–676
10. Nathan DM, Buse JB, Kahn SE, et al.; GRADE Study Research Group. Rationale and design of the Glycemia Reduction Approaches in Diabetes: a Comparative Effectiveness Study (GRADE). Diabetes Care 2013;36:2254–2261
11. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl. 1):S55–S64
12. Tung EL, Davis AM, Laiteerapong N. Glycemic control in nonpregnant adults with type 2 diabetes. JAMA 2018;319:2430–2431
13. Abbasi J. For patients with type 2 diabetes, what's the best target hemoglobin A1C? JAMA 2018;319:2367–2369
14. Bosi E, Dotta F, Jia Y, Goodman M. Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus. Diabetes Obes Metab 2009;11:506–515
15. Fujioka K, Brazg RL, Raz I, et al. Efficacy, dose-response relationship and safety of once-daily extended-release metformin (Glucophage XR) in type 2 diabetic patients with inadequate glycaemic control despite prior treatment with diet and exercise: results from two double-blind, placebo-controlled studies. Diabetes Obes Metab 2005;7:28–39
16. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE; Sitagliptin 036 Study Group. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care 2007;30:1979–1987
17. Grant PJ. The effects of high- and medium-dose metformin therapy on cardiovascular risk factors in patients with type II diabetes. Diabetes Care 1996;19:64–66
18. Lewin A, Lipetz R, Wu J, Schwartz S. Comparison of extended-release metformin in combination with a sulfonylurea (glyburide) to sulfonylurea monotherapy in adult patients with type 2 diabetes: a multicenter, double-blind, randomized, controlled, phase III study. Clin Ther 2007;29:844–855
19. Williams-Herman D, Johnson J, Teng R, et al. Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. Diabetes Obes Metab 2010;12:442–451
20. Frias JP, Zimmer Z, Lam RLH, et al. Double-blind, randomized clinical trial assessing the efficacy and safety of early initiation of sitagliptin during metformin uptitration in the treatment of patients with type 2 diabetes: the CompoSIT-M study. Diabetes Obes Metab 2019;21:1128–1135
21. Filozof C, Schwartz S, Foley JE. Effect of vildagliptin as add-on therapy to a low-dose metformin. World J Diabetes 2010;1:19–26
22. Weissman P, Goldstein BJ, Rosenstock J, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. Curr Med Res Opin 2005;21:2029–2035
23. Gale EA, Beattie SD, Hu J, Koivisto V, Tan MH. Recruitment to a clinical trial improves glycemic control in patients with diabetes. Diabetes Care 2007;30:2989–2992
24. Williams LK, Padhukasahasram B, Ahmedani BK, et al. Differing effects of metformin on glycemic control by race-ethnicity. J Clin Endocrinol Metab 2014;99:3160–3168
25. Diabetes Prevention Program Research Group. Long-term effects of metformin on diabetes prevention: identification of subgroups that benefited most in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. Diabetes Care 2019;42:601–608
26. Goonesekera SD, Yang MH, Hall SA, Fang SC, Piccolo RS, McKinlay JB. Racial ethnic differences in type 2 diabetes treatment patterns and glycaemic control in the Boston Area Community Health Survey. BMJ Open 2015;5:e007375
27. McGovern A, Tippu Z, Hinton W, Munro N, Whyte M, de Lusignan S. Comparison of medication adherence and persistence in type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2018;20:1040–1043
28. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) [published correction appears in Lancet 1998;352:1558]. Lancet 1998;352:854–865
29. Holstein A, Egberts EH. Risk of hypoglycaemia with oral antidiabetic agents in patients with type 2 diabetes. Exp Clin Endocrinol Diabetes 2003;111:405–414
30. Lalau JD, Race JM, Brinquin L. Lactic acidosis in metformin therapy. Relationship between plasma metformin concentration and renal function. Diabetes Care 1998;21:1366–1367
31. Yang PK, Hsu CY, Chen MJ, et al. The efficacy of 24-month metformin for improving menses, hormones, and metabolic profiles in polycystic ovary syndrome. J Clin Endocrinol Metab 2018;103:890–899
32. Hanas R, John G; International HBA1c Consensus Committee. 2010 consensus statement on the worldwide standardization of the hemoglobin A1C measurement. Diabetes Care 2010;33:1903–1904
33. Hanas R, John WG; International HbA_1c Consensus Committee. 2013 update on the worldwide standardization of the hemoglobin A(1c) measurement. Clin Chem Lab Med 2013;51:1041–1042